Chapter

Ambulatory Isolated Systolic Hypertension and Cardiovascular Target Organ Damage in People of African Ancestry

Muzi Maseko, Bongubuhle Mlambo, Edgar Phukubje and Thamsanqa Nyundu

Abstract

Isolated systolic hypertension (ISH) is a major contributor to cardiovascular disease morbidity and mortality worldwide, however, diagnosis of ISH is mainly dependent on conventional blood pressure (BP) techniques. Studies that have used ambulatory blood pressure monitoring (ABPM) were only limited to 24-hour BP. To date ambulatory isolated BP subtypes have never been identified. Therefore, the prevalence of ambulatory subtypes of ISH unknown. Conventional and ambulatory BP was measure in 549 participants and based on the results, they were stratified into ISH subtypes (Conventional, Daytime, Night-time and 24-hour ISH). Participants further underwent measurements of pulse wave velocity (PWV) and left ventricular mass index (LVMI) to determine the extent of arterial stiffness and left ventricular hypertrophy. We further assessed whether the target organ changes are associated with any ISH subtype. The prevalence of Conventional ISH (ISHC), 24-hour ISH (ISH24), Night-time ISH (ISHN) and Daytime ISH (ISHD) was 7.5%, 7.1%, 7.7% and 7.5% respectively. Compared to normotensives, all ISH subtypes had higher PWV and LVMI. These target organ changes were similar to those observed in hypertensives. Our results indicate that isolated systolic hypertension, whether conventional or ambulatory, is as detrimental as hypertension on cardiovascular target organs.

Keywords: hypertension, hypertrophy, ambulatory nocturnal, conventional, cardiovascular

1. Introduction

By definition, hypertension is a chronic condition characterised by persistent elevated blood pressure [1]. Traditionally, the term hypertension has been used to describe a condition in which systolic BP (SBP) is equal or above 140 mm Hg and/or a diastolic BP (DBP) is equal or above 90 mm Hg [2]. The term Systolic-diastolic hypertension (SDH) is slowly replacing 'hypertension' in this regard as the latter becomes a broader term describing a large number of classes/categories of persistent high BP [3–5]. Thus hypertension can be divided into several types based on several criteria which may or may not overlap.

European Society of Cardiology/European Society of Hypertension (ESC/ESH) criteria for the classification of participants according to office (conventional) BP measurement [4].

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

The America College of cardiology/American Heart Society (ACC/AHA) has more stringent criteria for conventional BP diagnosis of the hypertension categories.

Category	SBP (mm Hg)		DBP (mm Hg)
Normal (Normotensive)	< 120	and	< 80
Elevated (High-Normal)	120–129	and	<80
Grade 1 Hypertension	130–139	and/or	80–90
Grade 2 Hypertension	≥ 140	and/or	≥ 90
Isolated Systolic Hypertensive	≥ 130	and	< 80
Isolated Diastolic Hypertension	< 130	and	≥ 80

The advent of ambulatory BP monitoring (ABPM) has revealed much about other subtypes of hypertension in everyday environments; in fact, some developed countries have called for the application of ABPM as a routine tool in clinical practice [6–9]. The superiority of this technique over office BP measurement has been well documented, particularly with respect to the prediction of cardiovascular events and target organ damage [10, 11]. Another benefit of this method is that it minimises the interference of false BP elevations/reductions that may be influenced by clinical settings or other stimuli, as the case may be with white coat hypertension or masked hypertension [10, 12].

The ABPM technique has been instrumental in the understanding of circadian rhythm of haemodynamics, in particular the phenomena of night-time BP dipping or rising, the early morning BP surge [13] as well as BP variability [8, 12]. In light of all these advantages, it is not surprising that ambulatory techniques are now considered the gold standard in hypertension diagnosis and out of office BP measurement [9, 14]. In fact, the ESH and ESC guidelines recommend that wherever possible this method be used as the basis for hypertension diagnosis [2].

The ESC/ESH and ACC/AHA thresholds for hypertension diagnosis according to ABPM [2, 15].

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

Using the above ambulatory blood pressure thresholds, the following subtypes of hypertension have been identified:

Hypertension subtype	Day BP (mm Hg)	Nigh BP (mm Hg)
Isolated Nocturnal Hypertension	< 135/85	≥ 120/70
Isolated Daytime Hypertension	≥ 135/85	< 120/70
Sustained 24-hour Hypertension	≥ 135/85	≥ 120/70

Ambulatory BP has also allowed identification of two abnormal night-time blood pressure patterns. The first one is an attenuated decline in nocturnal BP. Blood pressure varies over 24 hours, it is high during the day and low during the night. Normally, BP decreases by 10% to 20% during the night. Individuals that lack this decline in nocturnal BP are classified as non-dippers. A large body of evidence exists around the strong association between a non-dipping profile and target organ damage at a vascular, cardiac and cerebrovascular level. Another variant BP pattern that is opposite to non-dipping has been identified with ambulatory BP monitoring. Individuals who present with this condition have an abnormally high night-time BP that rises above the daytime BP values. This condition known as reverse dipping has also been associated with cardiovascular target organ damage.

1.1 Isolated systolic hypertension

Isolated Systolic Hypertension is a form of hypertension characterised by elevated SBP ≥ 140 mm Hg and often normal or low DBP < 90 mm Hg [16]. As a result of this, ISH is associated with increased pulse pressure (PP), which is the difference between SBP and DBP [16, 17]. Previous studies of ISH date as far back as 1970 [18], with interest in the subject increasing around the 1980's [19–22]. Most of these earlier studies identified ISH as a disease of the elderly, stemming from the "normal" physiological processes associated with ageing [20, 22, 23]. More recent studies have revealed that ISH does in fact also exist in younger individuals [24–27]. In either age group the condition can have detrimental effects on the cardiovascular system and other vital organs [12, 26, 28].

Systolic BP and PP are both increased in ISH, and are major predictors of heart disease. These haemodynamic parameters are associated with increased risk of myocardial infarction, left ventricular hypertrophy (LVH), renal dysfunction, stroke and cardiovascular mortality to a greater extent than DBP [29–31]. Some data from clinical trials suggest that even small elevations of SBP confer a significant risk of coronary heart disease [32]. The low DBP associated with ISH may lead to impaired tissue perfusion, particularly of the heart itself [29, 31]. In fact, ISH, which was long believed to be a normal and physiologically harmless state associated with the ageing process [30] has been shown to be a stronger predictor of cerebrovascular and cardiovascular events [32] as well as renal disease [29] than elevated DBP. A thorough understanding of the pathophysiology of ISH is necessary in order to manage the condition effectively and possibly reduce its negative effects on target organs.

Systolic BP has been shown to increase with age [33], a phenomenon that has been attributed to "natural" changes occurring in the arterial walls as the body ages. For this reason, most of the physiological mechanisms that are believed to be responsible for ISH are associated with the vascular ageing process [34]. This involves an interplay of several processes typically culminating in increased stiffness of the central arteries [30, 31, 35, 36].

As the vascular system ages - usually from about the age of 50 [17, 30], the arterial walls experience fatigue and the elastin fibres therein begin to fragment. This

is associated with increased calcium deposition and subsequent media calcification [17]. In addition to this, more collagen fibres are deposited into this fragile wall. There is an accumulation of Advanced Glycation End products (AGEs), which progressively and irreversibly interlink with collagen and elastin fragments to form a complex matrix [36, 37]. Local inflammation occurs, characterised by the release of pro-inflammatory cytokines and enzymes including some metalloproteases which inhibit the production of Nitric Oxide (NO) an influential vasodilator substance, leading to endothelial dysfunction [35, 36, 38].

The pathophysiology of ISH in young individuals is thought to differ at least to some extent from the mechanisms described for the older population [24, 28]. In some young people, ISH develops following a hyperkinetic pre-hypertensive state which is associated with an increase in sympathetic stimulation. This is associated with adrenergic activation with the release of norepinephrine. In these individuals, an increase in resting heart rate and cardiac output leads to an acceleration of arterial stiffness with an isolated increase of SBP [28]. The findings of McEniery et al. [39] in a study of individuals between 17 and 27 suggest that indeed aortic stiffness is associated with ISH in young people, having similar pathophysiological implications as it does in the elderly. Some researchers have shown that an increase in stroke volume in certain young individuals is the major contributor to an elevated PP leading to premature aortic stiffening [26, 27, 28, 39]. Increased body fat in obese young adults could also be a contributing factor to isolated elevation of SBP as the former has been shown to be a strong predictor of aortic stiffness [24].

Another type of ISH is observed in young active, particularly athletic adults. In this group, the SBP and PP elevations are often isolated to the peripheral arteries (especially in the upper limbs), while central haemodynamics remain normal [28, 40]. This phenomenon has been attributed to the effects of exercise-related bradycardia on stroke volume; which is thought to increase PP by exaggerating the amplification of the pressure wave [28, 40, 41]. This type of ISH is arguably considered spurious and somewhat 'non-detrimental' by most researchers [28, 42–44] since most risk is often associated with central rather than peripheral abnormalities [27].

1.2 Ambulatory isolated systolic hypertension

Early studies into ambulatory ISH seemed to suggest that ISH was a form of "white coat" hypertension that was not sustained during day to day activities outside a clinical setting [45, 46]. The work of Staessen et al. [10] compared the predictive ability of ABPM over conventional BP measurement in older ISH patients, and found that ambulatory SBP was a more superior predictor of cardiovascular risk than conventional SBP. Later research using improved technology for ABPM showed that while this may be true to some extent, sustained and masked forms of ISH are also prevalent, particularly in the elderly population [47]. Over time, ABPM became more useful in investigating ISH from several angles. It has been used to investigate postprandial hypotension in elderly ISH patients [48]. Saladini et al. [49] investigated the future risk of sustained hypertension in young, sporty ISH patients diagnosed by ABPM. These studies either used ABPM in people already diagnosed with ISH using conventional BP monitoring or diagnosed ISH with ABPM using only 24-hour BP. None these studies identified the ambulatory ISH subtypes. Therefore, a possibility exists that with ambulatory BP monitoring, different types of ISH can be identified.

With this gap in the current literature, we designed a study using ambulatory BP monitoring, with the aim of identifying different ambulatory ISH subtypes,

determining their prevalence and investigating whether these subtypes are associated with preclinical cardiovascular pathology in a population of African ancestry.

2. Methods

2.1 Study group

Participants of African ancestry were recruited from Soweto, a township in the southwest of Johannesburg. The lower age limit for the participants was 18 years and there was no upper age limit. Based on their conventional and ambulatory BP measurements were divided into the following six groups:

i. Normotensives (NT). Those with normal daytime and normal night-time ambulatory BP (daytime BP < 135/85 mm Hg and nighttime BP < 120/70 mm Hg).

ii. Hypertensives (HT). Those with increased daytime BP and increased night-time BP (daytime BP ≥ 135/85 mm Hg and night-time BP ≥ 120/70 mm Hg).

iii. Conventional isolated systolic hypertensives (ISHC). Those with increased conventional systolic BP and normal conventional diastolic BP (systolic BP ≥ 140 mm Hg and diastolic BP < 90 mm Hg).

iv. Twenty four-hour ambulatory isolated systolic hypertension (ISH24). Those with increased 24-hour systolic BP and normal 24-hour diastolic BP (24-hour systolic BP ≥ 130 mm Hg and 24-hour diastolic BP < 80 mm Hg).

v. Night-time isolated systolic hypertensives (ISHN). Those with increased night-time systolic BP and normal night-time diastolic BP (night-time systolic BP ≥ 120 and night-time diastolic BP < 70 mm Hg).

vi. Daytime isolated systolic hypertensives (ISHD). Those with increased daytime systolic BP and normal daytime diastolic BP (daytime systolic BP ≥ 135 mm Hg and daytime diastolic BP < 85 mm Hg).

2.2 Blood pressure measurement

Participants were invited to visit the Human Nutrition Clinic at the School of Physiology, Wits Medical School where conventional BP was measured using an automated pressure monitor (Omron, Kyoto, Japan) after they were allowed to rest for 10 minutes. Twenty four-hour ambulatory BP was measured using a 24-hour BP monitor (Spacelab, model 91207). Monitors were set to measure BP every 15 minutes from 06:00–22:00 and every 30 minutes thereafter until 06:00 the next morning. On average, participant bedtime was 19:00 and wake up time was 05:00. Based on this, the 09:00–19:00 and 23:00–05:00 intervals were used to define daytime and night time respectively.

2.3 Anthropometric measurements

Anthropometric measurements were taken while the participants were barefoot and wearing lightweight indoor robes. Weight was measured using a floor scale

(Health o meter® Professional, USA) and was recorded to the nearest 0.1 kg. For this measurement, the participant was asked to stand upright on the middle of the scale with their weight distributed evenly between both feet. Height was measured to the nearest 0.1 m using a wall-mounted stadiometer (Seca®, Germany), with the participant standing upright and the headpiece of the stadiometer was placed horizontally on the vertex (highest point) of the participant's head and the corresponding reading was recorded. Body Mass Index (BMI) was calculated as weight in kilogrammes divided by the square of the height in metres. Participants with a BMI $\geq$ 25 kg/m^2 were considered overweight, and those with a BMI $\geq$ 30 kg/m^2 were considered obese. Waist circumference was measured in at the end of normal expiration using an inextensible measuring tape aligned parallel to the floor at the narrowest point between the costal margin and the upper iliac crest.

2.4 Pulse wave velocity measurement

A high fidelity tonometer interfaced with a SphygmoCor computer software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia - version 9.0) was used to perform pulse wave assessments of pulse wave velocity (PWV), an index of arterial stiffness. Participants were allowed to rest in the supine position for 15 minutes prior to assessment. Using an inextensible measuring tape, distances (in mm) between the relative sampling sites (femoral and carotid) and the suprasternal notch were measured. The difference between the two distances was considered as the pulse wave distance. Applanation tonometry was then used to record sequential wave forms at the participant's dominant carotid and femoral regions. A three lead chest ECG was performed concurrently with the waveform sampling in order to assess the time differences in the generation of the waveforms. The pulse transit time was defined as the average of 10 consecutive beats. The PWV was automatically calculated as the difference between the aforementioned distances (i.e. the pulse wave distance) divided by the pulse transit time.

2.5 Echocardiography

Echocardiography was used to determine the left ventricular mass index for the participants. All echocardiographic measurements were carried out by an experienced technician using an echocardiogram - the Acuson SC2000 Diagnostic Ultrasound System (Siemens Medical Solutions USA, Inc.) linked to a 10-MHz linear array transducer and electrocardiogram. Participants were asked to lie in the left lateral decubitus position. M-mode images were taken at a frame rate of >110 frames per second. M-mode echocardiography of the short axis of the heart was obtained as close to the tip of the mitral valve as possible using the parasternal long axis view (2D). The resulting images were used to measure left ventricular dimensions only when the endocardial surfaces of the septal and posterior walls, as well as both the left and right septal surfaces, could be clearly seen. Wall dimensions, namely the Left Ventricular Internal Diameter at end Diastole (LVIDD), the Posterior Wall Thickness in Diastole (PWTD) and the Interventricular Septal Thickness in Diastole (IVSTD) were obtained from M-mode images. Left ventricular mass values were indexed for body.

3. Statistical analysis

Database management and statistical analyses were performed with SAS software, version 9.4 (The SAS Institute Inc., Cary, North Carolina, USA). Data

from individual subjects were averaged and expressed as mean ± SD for continuous variables and categorical variables were expressed as percentages. The differences between the means was calculated using the General Linear Model (GLM) and adjustments were made for the following covariates; age, gender, BMI, alcohol intake and cigarette smoking. A p value <0.05 was considered significant. The Receiver Operator Characteristics (ROC) curve analysis was used to determine how well the different subgroups of ISH would predict an increased PWV and LVMI. The ROC curve analysis is used in clinical prediction to assess how well a test can discriminate between absence or presence of a condition. The analysis yields a curve of sensitivity versus 1-specificity, where the Area Under the Curve (AUC) is a measure of predictive power of the test to a maximum of 1 [50]. The closer the AUC is to 1, the greater the ability of the test in question to discriminate whether the presence of a condition is associated with a change in a given parameter [50].

4. Results

Table 1 shows the demographic, general and clinical characteristics of the population under study. Of the 549 participants, 41 (7.5%) had ISH as measured by conventional means (ISHC). This figure is similar to those obtained for the ambulatory sub-types of ISH, namely 24-hour, Night-time and Daytime ISH which had 39 (7.1%), 42 (7.7%) and 41 (7.5%) participants respectively. Systolic-diastolic hypertension was observed in 161 (29%) of the participants. The mean age of the population was 45.3 ± 18.5 years and the ISHC group was significantly older (65.3 ± 13.5 years) than both normotensives (39.7 ± 17.6 years) and hypertensives (52.1 ± 15.5 years). There were slight reductions in average age within the other ISH subtypes, with ISH24 at 57.8 ± 20.1 years, ISHN at 55.4 ± 24.6 years and ISHD at 53.7 ± 20.9 years. We observed that all the ISH subgroups had greater proportions of female participants than the normotensive or hypertensive groups [51]. Anthropometry revealed significantly higher waist circumference in the ISHC group than in the normotensives, this was also true for all the other ISH subgroups albeit of no known significance. In addition to this, the overall population was overweight with a BMI of 29.1 ± 7.8 kg/m^2. Both ISHC and hypertensives were obese (BMI of 31.4 ± 7.5 kg/m^2 and 30.9 ± 7.5 kg/m^2 respectively), the former group having a significantly higher BMI than the normotensives (BMI = 28.0 ± 7.7 kg/m^2). The average SBPC of the ISHC group (153.1 ± 11.7 mm Hg) was higher than that of the hypertensive group (149.6 ± 20.3 mm Hg), and significantly higher than that of the normotensives (129.7 ± 21.4 mm Hg). Overall, the SBPC values for all ISH sub-types were high. Conventional ISH had an average DBPC of 83.5 ± 4.8 mm Hg, significantly higher than that of normotensives (77.6 ± 7.2 mm Hg) and significantly lower than that of hypertensives (98.6 ± 8.4 mm Hg). Similarly, 24-hour, night-time and daytime ISH all had conventional diastolic blood pressures below those of hypertensives but above those of normotensives. All sub-types of ISH had higher pulse pressure values than both normotensives and hypertensive groups, significantly so for those participants with ISHC (PP = 69.7 ± 12.3 mm Hg).

Tables 2 and **3** show the ROC curve analysis of the relationships between the sub-types of ISH and cardiovascular target organ changes. All subtypes of ISH were significantly associated with increased PWV and LVMI. Conventional ISH strongly predicts arterial stiffness and left ventricular hypertrophy, with area under the curve (AUC) values of 0.88 ± 0.03 (CI: 0.83 to 0.93) and 0.86 ± 0.03 (CI: 0.88 to 0.92), respectively. Daytime ISH was shown to be a strong predictor of both (PWV and LVMI) with all the values exceeding 0.8. all three organ changes under study

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

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

Table 1.
Demographic and clinical characteristics of participants according to blood pressure status.

ISH subtype	AUC	CI
ISHC	0.88±0.03	0.83 to 0.93
ISH24	0.77±0.04	0.68 to 0.86
ISHN	0.78±0.04	0.70 to 0.85
ISHD	0.83±0.05	0.74 to 60.92

AUC, area under the curve; CI, confidence intervals; ISHC, conventional isolated systolic hypertension; ISH24, 24 hour Isolated systolic hypertension; ISHN, Night-time isolated systolic hypertension; ISHD, Daytime isolated systolic hypertension P < 0.05 for all associations. Adjustments were made for age, gender, BMI, the use of antihypertensive medication, smoking and alcohol consumption.

Table 2.
ROC curve analysis of the relationship between ISH and PWV.

ISH subtype	AUC	CI
ISHC	0.86±0.03	0.88 to 0.92
ISH24	0.76±0.03	0.67 to 0.86
ISHN	0.71±0.05	0.62 to 0.80
ISHD	0.80±0.06	0.68 to 0.09

AUC, area under the curve; CI, confidence intervals; ISHC, conventional isolated systolic hypertension; ISH24, 24 hour Isolated systolic hypertension; ISHN, Night-time isolated systolic hypertension; ISHD, Daytime isolated systolic hypertension. P < 0.05 for all associations. Adjustments were made for age, gender, BMI, the use of antihypertensive medication, smoking and alcohol consumption.

Table 3.
ROC curve analysis of the relationship between ISH and LVMI.

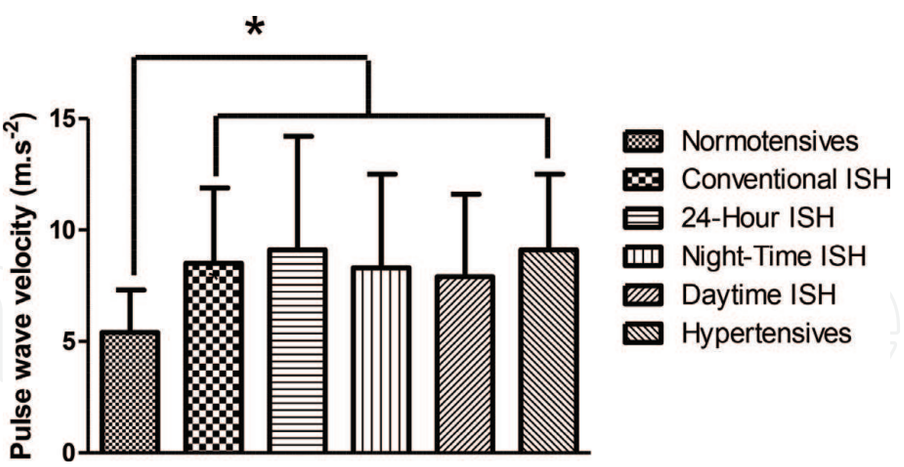

Figure 1.
*Comparison of PWV of ISH subgroups, the hypertensives and the normotensives. This figure shows data of PWV expressed as adjusted means ± SD. The differences between the means was calculated using the general linear model and adjustments were made for the following covariates; age, gender, BMI, alcohol intake and cigarette smoking. There was no significant difference in the PWV of the different ISH subtypes and none of the ISH subtypes was significantly different from the hypertensives. However, the PWV of all the ISH subtypes and hypertensives was significantly higher than that of the normotensives. * = p value <0.05.*

(AUC values all exceeding 0.8). The pattern of association and the significance was maintained even after adjusting for confounding variables.

Figures 1 and **2** shows data of PWV and LVMI respectively expressed as adjusted means ± SD. For both PWV and LVMI, there was no significant difference in the PWV of the different ISH subtypes and none of the ISH subtypes was

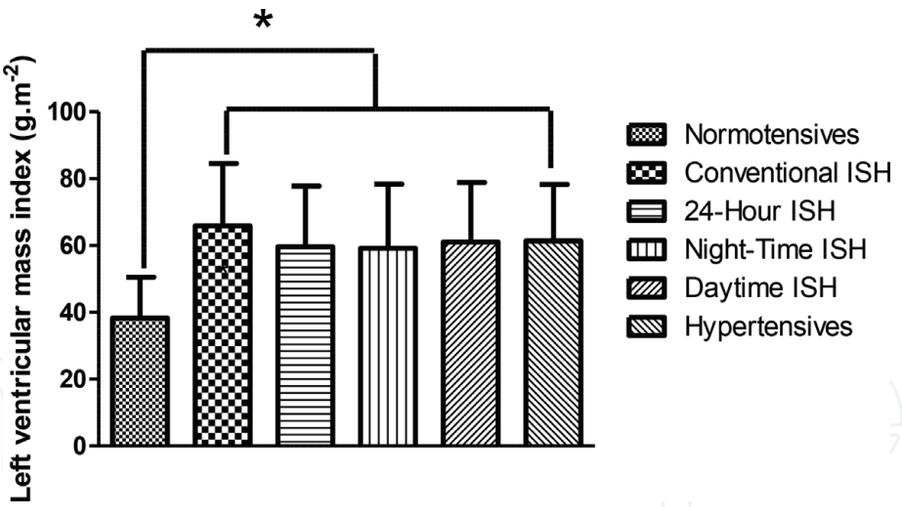

Figure 2.
*Comparison of the LVMI of the ISH subtypes, the normotensives and the hypertensives. This figure shows data of LVMI expressed as adjusted means ± SD. The differences between the means was calculated using the general linear model and adjustments were made for age, gender, BMI, alcohol intake, cigarette smoking and presence of diabetes. There was no significant difference in the LVMI of the different ISH subtypes and none of the ISH subtypes was significantly different from the hypertensives. However, the LVMI of all the ISH subtypes and hypertensives was significantly higher than that of the normotensives. * = p value <0.05.*

significantly different from the hypertensives. However, the PWV and LVMI of all the ISH subtypes were significantly higher than that of the normotensives.

5. Discussion

In the present study, we determined the general characteristics of ISH and went on to divide it into four subtypes namely Conventional ISH, 24-hour ISH, Night-time ISH and Daytime ISH. We proceeded to investigate the associations between each of these subtypes with PWV and LVM. We further investigated the extent to which each of the ISH subtypes predicted the target organ changes mentioned. The results of the present study show that 7.5% of the cohort had ISHC and the same percentage had Daytime ISH. Night-time ISH was found in 7.7% of the population, while 7.1% of the participants had 24-hour ISH. Furthermore, our findings show that all subtypes of ISH are significantly associated with increased PWV and LVMI in measures comparable to general hypertension, The percentage of participants with ISHC in our study is consistent with the work of Gupta *et al.,* [52] who found a similar (7.78%) prevalence of the condition following their study of office workers in a North Indian town. Huang *et al.,* [53] also found a similar prevalence of ISH (7.6%) in a Chinese study. However, all these studies used only conventional BP measurements to determine the prevalence of ISH. Hence our study is the first to identify the three ISH subtypes identified by ambulatory BP monitoring.

5.1 Determinants of ISH

5.1.1 Socio-economic status

Our and other studies indicate that the prevalence of isolated systolic hypertension averages around 8% across populations whether measured by conventional or ambulatory BP techniques. However, Ntuli, et al. [54] investigated a population ethnically similar to our study cohort and their study revealed a much higher

prevalence of ISHC (21%). The most likely explanation for this is the socioeconomic difference between their sample population and ours. The study by Ntuli et al. [54] was conducted in rural Limpopo (Dikgale), where unemployment and poverty is high and there is limited access to adequate healthcare [54–56]. Ntuli's study indicates that socio-economic factors could play a role in the prevalence of ISH. Socioeconomic factors have been implicated in contributing to the high prevalence of hypertension in developing countries [57, 58], and it would not be surprising that ISHC would follow the trend.

5.1.2 Age

The mean age of participants in the present study (45.3 years) was similar to that of subjects in the study by Ntuli et al. [54] (44.2 years). Gupta et al. [52] did not report a mean age for their population which was limited to the working age-group under 58 years, while Huang et al. [53] carried out their investigation on participants in the 35–74 age group [52, 53]. The bulk of studies on ISHC have been focused on specific age groups, usually the young (under 35 years of age) or the old (over 50 years old) [27, 49, 59, 60] unlike our population which included all consenting persons over the age of 18. While several studies in recent years have shown that the condition is not at all restricted to the older population [25–27], the relatively high average age associated with ISH (especially the conventional subtype) in our study is consistent with the findings of a number of researchers and with the widely accepted notion that ISH is predominant and naturally occurring in the elderly population [1, 16, 18, 30, 61]. A study by Huang et al. [53] also showed an increase in ISHC with age.

Martins et al. [62] observed an increase in PP and SBP from the age of 45 upward in their analysis of data from the NHANES. Indeed, the most commonly described pathophysiological mechanism for ISH involves changes occurring to the large arteries owing to ageing [13]. With age progression, elastin in the media decreases, leading to a fragmented media [13, 18] which is susceptible to calcium and lipid accumulation. Along with this media calcification occurs the accumulation of smooth muscle cells within the intima, collagen cross linking occurs and all this leads to the thickening and fibrosis of the arterial wall [13, 18, 43]. These changes culminate in arterial stiffness, an increased wall-to-lumen ratio and a reduced cross-sectional area of the lumen of the greater arteries [13, 37, 63]. Due to poor compliance, the large arteries fail to expand and subsequently recoil effectively in systole and diastole of the cardiac cycle, respectively. There is a resultant increase in aortic PP and PWV. Consequently, the reflected wave which would normally return during diastole, returns during late systole and augments systolic pressure; SBP increases while the DBP decreases [43, 63]. In line with this, we observed higher values of average SBPC in the ISH groups than in the normotensive group, and these were comparable to that of hypertensive participants. This was coupled with relatively low DBPC for all ISH sub-types when compared to the hypertensive group. By definition, PP is the difference between SBP and DBP, thus its normal value is approximately 40 mm Hg [64]. Pulse Pressure values exceeding 60 mm Hg are associated with target organ damage which may or may not be asymptomatic [3]. In the present study, PP was markedly increased in participants with ISHC, with an average of 69.7 mm Hg. Wallace et al. [65] also observed similar elevated SBP and PP (67 mm Hg) in their ISHC group. This finding was as expected based on the definition and underlying physiology of the condition [16, 18, 61] since PP is the difference between systolic and diastolic BPs; and an increase in the former and/or decrease in the latter would raise PP.

5.1.3 Obesity

In general, all the ISH groups in this study were obese. Average BMI values ranging from 30.9 to 31.4 were recorded for these groups, all of which exceed the obesity threshold of 30 for BMI [66]. The role of obesity as a risk factor for ISH is well documented [25, 35, 57, 63, 67]. Erhun et al. [68] observed the highest prevalence of ISH among the extremely obese group in their study. The ISH subgroup in the research by Grebla et al. [24] was overweight, and these authors suggested that obesity may be an important determinant of ISH in young adults [25]. A study by Nemes et al. [69] showed that obesity is associated with increased arterial stiffness and that this is true even for young obese adults, whose arterial stiffness they found comparable to that of elderly non-obese individuals. Although all of these studies investigated obesity in ISH by conventional BP measurement, their findings may extend to all the ambulatory subtypes of the condition as well. Our results show that in all participants with any forms of ISH, arterial stiffness as measured by PWV was increased in comparison to normotensives.

Several mechanisms have been described that may explain the role of obesity in ISH. Hyperinsulinaemia and insulin resistance, which are both strongly associated with obesity [70], may mediate aortic stiffness through glycation of vascular wall proteins and subsequent increased cross-linking [69]. Insulin has also been associated with smooth muscle hypertrophy and increased endothelial dysfunction of large arteries likely resulting from oxidant stress, causing increased susceptibility to atherosclerosis [69, 71]. One other significant mechanism that has been implicated in the relationship between obesity and ISH is the activity of leptin [69]. Hyperleptinaemia is associated with endothelial dysfunction in obese individuals [72], which is an underlying cause of arterial stiffness. Schutte et al. [73] reported a strong negative correlation between leptin and arterial compliance coupled with a strong positive relationship between leptin and SBP as well as leptin and PP in obese/overweight hypertensive African women. The high-leptin state of overweight/obese women in our study population, which was predominantly African, has been previously described [74] and may play an important role in ISH.

5.2 Isolated systolic hypertension target and target organ changes

5.2.1 Arterial stiffness

We measured PWV by applanation tonometry, a minimally invasive method which is widely recognised as the 'gold standard' in the determination of arterial stiffness [65, 75]. As far as we know there are no studies which have investigated PWV in ambulatory subtypes of ISH, however, the general association of ISHC with arterial and aortic stiffness has been reported [65, 76, 77]. Antza et al. [77] in their study of arterial stiffness in ISHC observed an increase in arterial stiffness in patients with the condition, and suggested that ISHC may have a role to play in large artery arteriosclerosis.

This observation can be explained in terms of the haemodynamic changes associated with ISH. Since ISH is characterised by elevated systolic and pulse pressures, these parameters exert increased mechanical stress on the arteries over time, leading to elastin fragmentation and subsequent calcification, collagen deposition and smooth muscle cell hypertrophy [34, 37, 76]. In addition to this, endothelial dysfunction associated with the shear stress also triggers the inhibition of NO production and the release of pro-inflammatory cytokines and growth factors such as TGF-β [31, 34, 65]. These augment arterial damage by promoting smooth muscle cell hypertrophy and the increased production of extracellular matrix proteins;

moreover, TGF-β inhibits the activity of those metalloproteases which would otherwise assist by breaking down the collagen build-up, such as MMP-9 [38]. All these factors culminate in arterial stiffening of mainly the central arteries. In essence, ISH speeds up the rate of arterial ageing and increases arterial stiffness, thereby leading to its own exacerbation in a vicious cycle [65]. Several scholars agree that the causal relationship between arterial stiffness and ISH is bidirectional [31, 34, 38].

With this in mind, it is not surprising that we observed significantly elevated PWV in all subtypes of ISH when compared to normotensives. Of interest, is that all ISH groups had an increase in PWV that is comparable to that of the sustained hypertensive group. This suggests that the arterial damage caused by the ISH groups may equal arterial stiffness arising from sustained hypertension in this population. This is contrary to our expectation. We expected the PWV of the ISH24 to be higher than that of the other groups due to the cumulative effects of a high systolic BP that is sustained over a 24-hout period. The explanation for this apparent discrepancy is that 24-hour BP is a combination of both daytime and night-time BP. Since BP decreases at night, that decline in nocturnal BP may have a damping effect on the *overall effect of ISH24 on arterial stiffness.

When we used ROC curve analysis to determine how well the different subgroups of ISH would predict an increased PWV in this population, our results indicate that all ISH subtypes predict PWV. Conventional ISH was the strongest predictor of arterial stiffness with an AUC of 0.88 followed by ISHD at 0.83. In this respect, daytime BP is emerging as the best predictor of ISH in this population as both conventional and daytime ambulatory BP are measured during the day. This is due to the 24-hour pattern of BP in which BP increases during the day and decreases at night. Our results indicate that the increase in daytime systolic BP in people with ISH is exaggerated, resulting in a high PP of 70 mmHg, which is 30 mm Hg the normal value of 40 mm Hg. This is PP value is higher than that of people with sustained hypertension. The same pattern was observed in people with ISHD. As discussed earlier, PP is an independent risk factor for vascular disease. This explains why ISHC and ISHD which have the highest PP, are the strongest predictors of arterial stiffness. Even though ISHN predicts arterial to a lesser extent than ISHC and ISHD, it is still a strong predictor of arterial stiffness with an AUC of 0.78. This highlights the importance of this study which is the first to discover the existence of this clinical entity.

5.2.2 Left ventricular hypertrophy

Left ventricular mass index has been used as an indication of LVH, a major independent predictor of cardiovascular mortality and morbidity [78–80]. We used echocardiography, a well-accepted, efficient and non-invasive tool for the estimation of LVMI [79, 80]. In this study, there were no clear differences in LVMI values obtained for the ambulatory ISH sub-types (ISHD, ISHN and ISH24), suggesting that there are no major differences in the development of LVH among these three subtypes; although the extent of cardiac damage they caused is similar to that associated with hypertension. This implies that even if diastolic BP can be normal, the impact of systolic BP alone is significant has a significant impact on cardiac morphology. The premature return of the reflected wave in ISH is probably the most significant cause of LVM increase [81] in this condition. The augmentation of SBP by the reflected wave results in an increased afterload to the left ventricle. As the left ventricle adapts to the increased workload, concentric hypertrophy of surrounding tissue occurs, resulting in thickening and increase in mass of the left ventricle wall [37]. Poor coronary perfusion owing to low DBP may also exacerbate the effects of increased LVM in ISH as increased oxygen demand of the myocardium

becomes difficult to meet [82]. Our results bear some similarity to those obtained by Pearson et al. [83], who reported that ISHC patients exhibited increased LVMI arising from thickened septal and posterior walls of the left ventricle. Lip et al. [84] had related outcomes, they found that LVMI and other echographic parameters were similar between ISHC and full hypertension (SDH) groups. Our study adds significantly to this body of knowledge by showing that ISH has a number of subtypes which are as detrimental to cardiac pathology as both ISHC and sustained hypertension. Some research has shown that increased LVMI even within the "normal" range is clinically relevant i.e. it is associated with significant cardiovascular risk [85]. Since ISH increases the risk of LVH at least twofold, even the preclinical increases in LVM observed in this study may progress to cardiac pathology over time as the elevated SBP persists.

Most ISH studies in the past have been carried out on elderly participants, however, our results show that even after correcting for age the associations and predictions remain unchanged, suggesting that ISH is just as detrimental to the elderly as it is to younger age groups with respect to left ventricle structure and consequently, cardiovascular function. Levy et al. [79] also found that the relationship between increased LVMI and cardiovascular morbidity and mortality was applicable to the middle-aged study group as much as the elderly study group, although their focus was not particularly on ISH. Obesity, which was identified in this ISH population, is thought to increase the risk of LVM and LVH by its tendency to attract other risk factors such as metabolic syndrome and diabetes mellitus [85]. Genetics also plays an important and complex role in the increase of LVM and development of LVH. So, the population under study - being predominantly black, may be at higher risk of LVH. Skelton et al. [86] reported a very high prevalence of increased LVM in an African-American population. This highlights the need for more studies to investigate the impact of ISH subtypes to be investigated.

Similar to PWV, again ISHC and ISHD were the strongest predictors of increased LVMI according to ROC analysis (AUC = 0.86 and 0.80 respectively), followed by ISH24 (AUC = 0.76) and ISHN (AUC = 0.71). This confirms the impact of the increases in daytime systolic BP on cardiovascular organs. There is no comparable research on ISH subtypes predictive power on increased LVMI, however our results provide strong evidence that ISH subtypes, which were not known previous to this study, predict preclinical cardiac pathology similar to hypertension, indicating that these subtypes are clinical entities that require intervention.

6. Conclusion

Our overall findings are that there are three subtypes of ambulatory ISH (24-hour ISH, night-time ISH and daytime ISH) which had not been previously defined. Night-time ISH is the most prevalent form of ISH in this population. Most importantly our results indicate that all these ISH subtypes may be as detrimental to cardiovascular organs as hypertension as they all emerged as good predictors of elevated PWV and LVMI, which are markers of arterial stiffness and left ventricular hypertrophy respectively. This highlights the importance of using both conventional and ambulatory BP techniques for the diagnosis ISH because current strategies that are limited to conventional BP monitoring, are incapable of detecting ambulatory isolated systolic hypertension subtypes. Moreover, since this data shows that night-time ISH is the most prevalent form of ISH, and it predicts both arterial stiffness and left ventricular hypertrophy, diagnosis of nocturnal ISH may be very essential in the management of BP related cardiovascular target organ damage.

Acknowledgements

The authors would like to acknowledge Mokgadi Maseko for her technical support and members of the Soweto community whose voluntary participation made this study possible.

Author details

Muzi Maseko*, Bongubuhle Mlambo, Edgar Phukubje and Thamsanqa Nyundu
University of the Witwatersrand, Johannesburg, South Africa

*Address all correspondence to: muzi.maseko@wits.ac.za

References

[1] Seedat YK, Rayner BL, Veriava, Y. South African Hypertension Practice Guideline 2014. Cardiovascular Journal of Africa. 2014; 25 (6): 288-294.

[2] Williams B, Mancia G, Spiering, W, Rosei, E.A, Azizi M, Burnier M, Clement D.L, Coca A, de Simone G, Dominiczak A. Kahan T. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Journal of hypertension. 2018;36(10): 1953-2041.

[3] Papademetriou V, Devereux RB, Narayan P, Wachtell K., Bella JN, Gerdts E, Chrysant SG, Dahlöf B.. Similar effects of isolated systolic and combined hypertension on left ventricular geometry and function: the LIFE Study. American journal of hypertension. 200;114(8): 768-774.

[4] Tsimploulis A, Sheriff, HM, Lam PH, Dooley, DJ, Anker, MS, Papademetriou V, Fletcher, RD, Faselis C, Fonarow GC, Deedwania P, White M. Systolic–diastolic hypertension versus isolated systolic hypertension and incident heart failure in older adults: Insights from the Cardiovascular Health Study. International journal of cardiology. 2017; 235: 11-16.

[5] Sulbaran TA, Silva ER, Maestre G. Isolated systolic hypertension: a new challenge in medicine. Journal of human hypertension. 2002; 16(1): 44-47.

[6] Pang TC, Brown MA. Accuracy of ambulatory blood pressure monitors in routine clinical practice. American journal of hypertension. 2006; 19(8): 801-809.

[7] Ommen ES, Schröppel B, Kim JY, Gaspard G, Akalin E, de Boccardo G, Sehgal V, Lipkowitz M, Murphy B. Routine use of ambulatory blood pressure monitoring in potential living kidney donors. Clinical Journal of the American Society of Nephrology. 2007; 2(5): 1030-1036

[8] O' Brien E, Dolan E. Ambulatory blood pressure measurement in the elderly. Hypertension. 2019; 73: 961-964.

[9] Bloch MJ, Basile JN. Ambulatory blood pressure monitoring to diagnose hypertension--an idea whose time has come. Journal of the American Society of Hypertension. 2016; 10(2): 89.

[10] Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, De Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Journal of the American Medical Association. 1999; 282(6): 539-546.

[11] Dolan E, Stanton AV, Thom S, Caulfield M, Atkins N, McInnes G, Collier D, Dicker P, O'Brien E. Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients – an Anglo-Scandinavian cardiac outcomes trial substudy. Journal of hypertension. 2009; 27(4): 876-885.

[12] Kocemba J, Kaweka-Jaszcz K, Gryglewska B, Grodzicki T. Isolated systolic hypertension: pathophysiology, consequences and therapeutic benefits. Journal of Human Hypertension. 1998; 12: 621-626.

[13] Snincak M, El-Abdin MZ, Hrabcakova P, Pella J, Kolesar K. Early Morning Surge Blood Pressure and Isolated Systolic Hypertension-A Clinical Importance in Elderly. Journal of Hypertension. 2018; 36: e179.

[14] Hodgkinson J, Mant J, Martin U, Guo B, Hobbs FDR, Deeks JJ, Heneghan C, Roberts N, McManus RJ. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. British Medical Journal 2011; 342: d3621.

[15] Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin E.J. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2018; 71(19): e127-e248.

[16] Hall WD. A rational approach to the treatment of Hypertension in special populations. American Family Physicia. 1999; 60(1): 156-162.

[17] Emeriau JP, Kalula SZ. Management of hypertension in older persons - specific considerations. CME: The SA Journal of CPD. 2013; 31 (10): 358-32.

[18] Colandrea MA, Friedman GD, Nichaman MZ, Lynd CN. Systolic hypertension in the elderly: an epidemiologic assessment. Circulation. 1970; 41(2): 239-245.

[19] Kannel, W.B., Dawber, T.R. and McGee, D.L., 1980. Perspectives on systolic hypertension. The Framingham study. Circulation, 61(6): 1179-1182.

[20] Kannel, W.B., Wolf, P.A., McGee, D.L., Dawber, T.R., McNamara, P. and Castelli, W.P., 1981. Systolic blood pressure, arterial rigidity, and risk of stroke: the Framingham study. Journal of the American Medical Association, 245 (12): 1225-1229.

[21] Curb, J.D., Borhani, N.O., Entwisle, G., Tung, B., Kass, E., Schnaper, H., Williams, W. And Berman, R., 1985. Isolated Systolic Hypertension in 14 Communities. American Journal of Epidemiology, 121(3): 362-370

[22] Saltzberg, S., Stroh, J.A. and Frishman, W.H., 1988. Isolated systolic hypertension in the elderly: pathophysiology and treatment. Medical Clinics of North America, 72(2): 523-547.

[23] Wilking, S.V.B., Belanger, A.L., Kannel, W.B., D'Agostino, R.B. and Steel, K., 1988. Determinants of isolated systolic hypertension. Journal of the American Medical Association, 260(23): 3451-3455.

[24] Grebla, R.C., Rodriguez, C.J., Borrel., L.N. and Pickering, T.G., 2010. Prevalence and Determinants of Isolated Systolic Hypertension among Young Adults: the 1999-2004 U.S. National Health and Nutrition Examination Survey. Journal of Hypertension, 28(1): 15-23.

[25] Jangid, P., Maheshwari, M., Tilwani, K., Nagal, M. and Soni, N.D., 2015. Isolated Systolic Hypertension in Young Healthy Adults – A review. Scholars Academic Journal of Biosciences, 3 (11): 919-921.

[26] Lurbe, E. and Redon, J., 2016. Isolated Systolic Hypertension in Young People is not Spurious and Should Be Treated. Hypertension, 68(2): 276-280.

[27] Eeftinck Schattenkerk, D.W., van Gorp, J., Vogt, L., Peters, R.J. and van den Born, B.J.H., 2018. Isolated systolic hypertension of the young and its association with central blood pressure in a large multi-ethnic population. The HELIUS study. European journal of preventive cardiology, 25(13): 1351-1359.

[28] Palatini, P., Rosei, E.A., Avolio, A., Bilo, G., Casiglia, E., Ghiadoni, L.,

Giannattasio, C., Grassi, G., Jelakovich, B., Julius, S. and Mancia, G., 2018. Isolated systolic hypertension in the young: a position paper endorsed by the European Society of Hypertension. Journal of hypertension, 36(6): 1222-1236.

[29] Chobanian, A.R., 2007. Isolated Systolic Hypertension in the Elderly. New England Journal of Medicine, 357(8): 789-796.

[30] Gavish, B. and Izzo Jr, J.L., 2016. Arterial stiffness: going a step beyond. American Journal of Hypertension, 29(11): 1223-1233.

[31] Cushman, W.C., 1998. The clinical significance of systolic hypertension. American journal of hypertension, 11(S8): 182S–185S.

[32] AlGhatrif, M. and Lakatta, E.G., 2015. The conundrum of arterial stiffness, elevated blood pressure, and aging. Current hypertension reports, 17(2): 12.

[33] Singh R. Isolated Systolic Hypertension. Medicine Update 2012; 22: 111-116.

[34] Park, J.B., Kario, K. and Wang, J., 2015. Systolic Hypertension: An increasing clinical challenge in Asia. Hypertension Research, 38: 227-236.

[35] Bavishi, C., Goel, S. and Messerli, F.H., 2016. Isolated systolic hypertension: an update after SPRINT. The American journal of medicine, 129(12): 1251-1258.

[36] Steppan, J., Barodka, V., Berkowitz, D.E. and Nyhan, D., 2011. Vascular stiffness and increased pulse pressure in the aging cardiovascular system. Cardiology research and practice, 2011.

[37] Ecobici, M. and Stoicescu, C., 2017. Arterial Stiffness and Hypertension–Which Comes First? Maedica, 12(3): 184.

[38] Schiffrin, E.L., 2004. Vascular stiffening and arterial compliance: implications for systolic blood pressure. American journal of hypertension, 17(S3): 39S–48S.

[39] McEniery, C.M., Yasmin, Wallace, S., Maki-Petaja, K., McDonnell, B., Sharman, J.E., Retallick, C., Franklin, S.S., Brown, M.J., Lloyd, R.C. and Cockcroft, J.R., 2005. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. Hypertension, 46(1): 221-226.

[40] Mahmud, A. and Feely, J., 2003. Spurious systolic hypertension of youth: fit young men with elastic arteries. American journal of hypertension, 16(3): 229-232.

[41] Bursztyn, M., 2018. Isolated systolic hypertension in young adults: a heterogeneous finding. Journal of hypertension, 36(9): 1791-1792.

[42] O'Rourke, M.F., Vlachopoulos, C. and Graham, R.M., 2000. Spurious systolic hypertension in youth. Vascular medicine, 5(3): 141-145.

[43] Hulsen, H.T., Nijdam, M.E., Bos, W.J., Uiterwaal, C.S., Oren, A., Grobbee, D.E. and Bots, M., 2006. Spurious systolic hypertension in young adults; prevalence of high brachial systolic blood pressure and low central pressure and its determinants. Journal of hypertension, 24(6): 1027-1032.

[44] Krzesinski, J.M. and Saint-Remy, A., 2006. Spurious systolic hypertension in youth: what does it really mean in clinical practice? Journal of hypertension, 24(6): 999-1001.

[45] Silagy, C.A., McNeil, J.J. and McGrath, B.P., 1990. Isolated systolic hypertension: does it really exist on ambulatory blood pressure monitoring? Clinical and Experimental Pharmacology and Physiology, 17(3): 203-206.

[46] Sega, R., Cesana, G., Milesi, C., Grassi, G., Zanchetti, A. and Mancia, G., 1997. Ambulatory and home blood pressure normality in the elderly: data from the PAMELA population. Hypertension, 30(1): 1-6.

[47] Franklin, S.S., 2012. Elderly Hypertensives: How Are They Different? Journal of Clinical Hypertension, 14(11): 779-786.

[48] Grodzicki, T., Rajzer, M., Fagard, R., O'Brien, E.T., Thijs, L., Clement, D., Davidson, C., Palatini, P., Parati, G., Kocemba, J. and Staessen, J.A., 1998. Ambulatory blood pressure monitoring and postprandial hypotension in elderly patients with isolated systolic hypertension. Journal of human hypertension, 12(3): 161-165.

[49] Saladini, F., Fania, C., Mos, L., Garavelli, G., Mazzer, A. and Palatini, P., 2018. Risk of Developing Sustained Hypertension in Isolated Systolic Hypertension of the Young Identified with Ambulatory Blood Pressure Monitoring. Journal of Hypertension, 36: e7.

[50] Chung, C.M., Cheng, H.W., Chang, J.J., Lin, Y.S., Hsiao, J.F., Chang, S.T. and Hsu, J.T., 2014. Relationship between resistant hypertension and arterial stiffness assessed by brachial-ankle pulse wave velocity in the older patient. Clinical interventions in aging, 9: 1495.

[51] Maseko J., Woodiwiss A., Majane O., Libhaber C., Brooksbank R., Norton G. Journal of Hypertension 2013. 31 (7): 1379-1386.

[52] Gupta, A.K., Negi, P.C., Gupta, B.P., Bhardwaj, A. and Sharma, B., 2006. Isolated Systolic Hypertension among Office Workers in North Indian Town. Indian Journal of Community Medicine, 31(2): 109-110.

[53] Huang, J., Wildman, R.P., Gu, D., Muntner, P., Su, S. and He, J., 2004. Prevalence of isolated systolic and isolated diastolic hypertension subtypes in China. American Journal of Hypertension, 17 (10): 955-962.

[54] Ntuli, S.T., Maimela, E., Alberts, M., Choma, S. and Dikotope, S., 2015. Prevalence and Associated Risk Factors of Hypertension amongst adults in a rural community of Limpopo Province, South Africa. African Journal of Primary Healthcare and Family Medicine, 7(1): 1-5.

[55] Alberts, M., Urdal, P., Steyn, K., Stensvold, I., Tverdal, A., Nel, J.H. and Steyn, N.P., 2005. Prevalence of cardiovascular diseases and associated risk factors in a rural black population of South Africa. European Journal of Cardiovascular Prevention & Rehabilitation, 12(4): 347-354.

[56] Kanjala, C., Alberts, M., Byass, P. and Burger, S., 2010. Spatial and temporal clustering of mortality in Digkale HDSS in rural northern South Africa. Global Health Action, 3(1), 5236.

[57] Seedat, Y.K., 1999. Hypertension in black South Africans. Journal of Human Hypertension, 13: 97-103.

[58] Gómez-Olivé, F.X., Alix, S.A., Made, F., Kyobutungik, C., Nonterah, E., Micklesfield, L., Alberts, M., Boua, R., Hazelhurst, S., Debpuur, C, Mashinya, F., Dikotope, S., Sorgho, H., Cook, I., Muthuri, S., Soo, C., Mukomana, F., Agongo, G., Wandabwa, C., Afolabi, S., Oduro, A., Tinto, H., Wagner, R.G., Haregu, T., Wade, A., Kahn, K., Norris, S.A., Crowther, N.J., Tollman, S., Sankoh, O. and Ramsay, M., as members of AWI-Gen and the H3Africa Consortium, 2017. Regional and sex differences in the Prevalence and Awareness of Hypertension: An H3Africa AWI-Gen Study Across 6 Sites in Sub-Saharan Africa. Global Heart, 12 (2): 81-90.

[59] Ming, J., Sheng, L.L., Zhang, L.G., De Ren, Q., Xueyan, C., Fen,

Z.J., Ru, F.S. and Ling, W.S., 1993. Abnormal renal function in isolated systolic hypertension correlation with ambulatory blood pressure. International journal of cardiology, 41(1): 69-75.

[60] Chaudhry, S.I., Krumholz, H.M. and Foody, J.M., 2004. Systolic hypertension in older persons. Journal of the American Medical Association, 292(9): 1074-1080.

[61] Stokes, G.S., 2006. Treatment of Isolated Systolic Hypertension. Current Hypertension Reports, 8: 377-383.

[62] Martins, D., Nelson, K., Pan, D., Tareen, N. and Norris, K., 2001. The effect of gender on age-related blood pressure changes and the prevalence of isolated systolic hypertension among older adults: data from NHANES III. The Journal of Gender-specific medicine, 4 (3): 10-3, 20.

[63] Tan, J.L. and Thakur, K., 2019. Systolic Hypertension. In StatPearls [Internet]. StatPearls Publishing.

[64] Homan, T.D. and Cichowski, E., 2019. Physiology, pulse pressure. In StatPearls [Internet]. StatPearls Publishing.

[65] Wallace, S.M., Yasmin, McEniery, C.M., Mäki-Petäjä, K.M., Booth, A.D., Cockcroft, J.R. and Wilkinson, I.B., 2007. Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. Hypertension, 50(1): 228-233.

[66] Janssen, I., Katzmarzyk, P.T. and Ross, R., 2004. Waist circumference and not body mass index explains obesity-related health risk. The American journal of clinical nutrition, 79(3): 379-384.

[67] He, F.J., Markandu, N.D., MacGregor, G.A., 2005. Modest Salt Reduction Lowers Blood Pressure in Isolated Systolic Hypertension and Combined Hypertension. Hypertension, 46 (1): 66-70.

[68] Erhun, W.O., Olayiwola, G., Agbani, E.O. and Omotoso, N.S., 2005. Prevalence of hypertension in a university community in South West Nigeria. African Journal of Biomedical Research, 8:15-19

[69] Nemes, A., Gavallér, H., Csajbók, É., Forster, T. and Csanády, M., 2008. Obesity is associated with aortic enlargement and increased stiffness: an echocardiographic study. The international journal of cardiovascular imaging, 24(2): 165-171.

[70] Brunzell, J.D. and Hokanson, J.E., 1999. Dyslipidemia of central obesity and insulin resistance. Diabetes care, 22: C10.

[71] Arcaro, G., Cretti, A., Balzano, S., Lechi, A., Muggeo, M., Bonora, E. and Bonadonna, R.C., 2002. Insulin causes endothelial dysfunction in humans: sites and mechanisms. Circulation, 105(5): 576-582.

[72] Leung, Y. and Kwan, C., 2008. Dual vascular effects of leptin via endothelium: hypothesis and perspective. Chinese Journal of Physiology, 51(1): 1-6.

[73] Schutte, R., Huisman, H.W., Schutte, A.E. and Malan, N.T., 2005. Leptin is independently associated with systolic blood pressure, pulse pressure and arterial compliance in hypertensive African women with increased adiposity: the POWIRS study. Journal of human hypertension, 19(7): 535.

[74] Maseko, M., Mashao, M., Bawa-Allah, A., Phukubje, E., Mlambo, B. and Nyundu, T., 2018. Obesity masks the relationship between dietary salt intake and blood pressure in people of African ancestry: the impact of obesity on the relationship between sodium and blood

pressure. Cardiovascular journal of Africa, 29(3): 172-176.

[75] Stoner, L., Young, J.M. and Fryer, S., 2012. Assessment of Arterial Stiffness and Endothelial Function Using Pulse Wave Analysis. International Journal of Vascular Medicine, 2012.

[76] O'Rourke, M.F. and Nichols, W.W., 2005. Aortic Diameter, Aortic Stiffness, and Wave Reflection Increase with Age and Isolated Systolic Hypertension. Hypertension, 45(4): 652-658.

[77] Antza, C., Papakatsika, S., Dimopoulos, C., Mikoudi, K., Stabouli, S. and Kotsis, V., 2015. 7C. 01: Arterial Stiffness in Isolated Office Systolic Hypertension. Journal of hypertension, 33: e96.

[78] Savage, D.D., Garrison, R.J., Kannel, W.B., Levy, D., Anderson, S.J., Stokes, J.3., Feinleib, M. and Castelli, W.P., 1987. The spectrum of left ventricular hypertrophy in a general population sample: The Framingham Study. Circulation, 75(1): 26-33.

[79] Levy, D., Garrison, R.J., Savage, D.D., Kannel, W.B. and Castelli, W.P., 1990. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. New England Journal of Medicine, 322(22): 1561-1566.

[80] Ofili E.O., Cohen, J.D., Vrain, J.A.S., Pearson, A., Martin, T.J., Uy, N.D., Castello, R. and Labovitz, A.J., 1998. Effect of treatment of isolated systolic hypertension on left ventricular mass. Journal of the American Medical Association, 279(10): 778-780.

[81] Karpetas A, Sarafidis PA, Georgianos PI, Protogerou, A, Vakianis P, Koutroumpas G, Raptis V, Stamatiadis DN, Syrganis C, Liakopoulos V, Efstratiadis G. Ambulatory recording of wave reflections and arterial stiffness during intra-and interdialytic periods in patients treated with dialysis. Clinical Journal of the American Society of Nephrology. 2015; 10(4): 630-638.

[82] Nichols WW, Edwards DG. Arterial elastance and wave reflection augmentation of systolic blood pressure: deleterious effects and implications for therapy. Journal of cardiovascular pharmacology and therapeutics. 2001; 6(1): 5-21.

[83] Pearson AC, Gudipati C, Nagelhout D, Sear J, Cohen JD, Labovitz AJ. Echocardiographic evaluation of cardiac structure and function in elderly subjects with isolated systolic hypertension. Journal of the American College of Cardiology. 1991; 17(2): 422-430.

[84] Lip GY, Blann AD. and Beevers DG. Prothrombotic factors, endothelial function and left ventricular hypertrophy in isolated systolic hypertension compared with systolic-diastolic hypertension. Journal of hypertension. 1999; 17(8): 1203-1207.

[85] Foppa M, Duncan BB, Rohde LE. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy? Cardiovascular ultrasound. 2005; 3(1): 17.

[86] Skelton TN, Andrew ME, Arnett DK, Burchfiel CM, Garrison RJ, Samdarshi TE, Taylor HA, Hutchinson RG. Echocardiographic left ventricular mass in African-Americans: The Jackson cohort of the Atherosclerosis Risk in Communities Study. Echocardiography. 2003; 20(2): 111-120.