

# Cardiovascular magnetic resonance characterisation of the phenotype of resistant uncontrolled hypertension

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**LTKPHE001**

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## Dedication

I would like to dedicate this paper to my late father, Ntate Alphonse Naleli Letuka (17.04.2001). He was a firm believer in education and hard work. To my mother, 'Me Poleliso Qhobela-Letuka, my sister, Lineo 'Mantee Tsiu, as well as the Qhobela and Letuka families for their support and encouragement throughout this journey. To my partner, Sera Falatsi and his family for their love and acceptance, to the late Falatsi Charles Falatsi and the late Dr Thato Hlothoane (07.04.2019), who passed shortly before this thesis was submitted. To all the young girls who have to work twice as hard, to the young girls from disadvantaged backgrounds, and to anyone in the minority, I hope this inspires you to persevere in the midst of adversity.

Lastly, I dedicate this to God in heaven, for being my source of strength and for affording me a privilege such as this one.

## Declaration

I, Pheletso Letuka, hereby declare that the work on which this dissertation/thesis is based on my original work (except where acknowledgements indicated otherwise). I declare that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I authorisethe University to reproduce for research either the whole or any portion.

Signature: 

Signed by candidate
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Date: 24/01/2020

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## Abstract

**Background:** Resistant hypertension (RH) is defined as blood pressure (BP) that remains elevated (>140/90mmHg) despite being treated with an antihypertensive regimen of 3 or more medications from different classes, including a long-acting calcium channel blocker, an angiotensin converting enzyme inhibitor or angiotension receptor blocker and a diuretic. The prevalence of RH in South Africa is currently unknown, however, clinical reports suggest that it is not rare. Patients with RH are significantly predisposed to cardiovascular (CV) diseases compared to patients with controlled BP. Consequences of RH include left ventricular hypertrophy, heart failure, ischaemic heart disease, chronic kidney disease leading to end-stage renal disease, stroke, vascular dementia, CV death and peripheral arterial disease. A proportion of patients with RH who never achieve BP control despite maximal medical treatment, represent a potentially novel and distinctive phenotype which is different from RH patients whose BP can be controlled. Recognising and categorising such patients becomes the initial and crucial step in stratifying phenotypes and defining mechanisms of treatment resistance.

**Objectives:** The aim of this study was to identify patients with resistant uncontrolled hypertension (RUH) and compare phenotypes in these patients to resistant controlled hypertensives (RCH).

**Methods:** We enrolled 50 patients from the Groote Schuur Hospital Hypertension Clinic: a tertiary referral hospital for RH. Patients on 4 or more antihypertensive medication including a diuretic, with BP <140/90mmHg were considered RCH, and those with BP  $\geq$  140/90 considered RUH. Assessments included clinical examination, electrocardiography, echocardiography, applanation tonometry, serum biomarkers and cardiovascular magnetic

resonance (CMR - which included biventricular volumes and function, myocardial strain, tissue characteristics and late gadolinium enhancement - LGE).

**Results:** Thirty were diagnosed with RUH and twenty with RCH. Patients with RUH were more likely to have a longer duration since diagnosis of hypertension ( $10.5 \pm 10.7$  vs.  $3.6 \pm 3.4$ ,  $p=0.02$ ) and more likely to be on treatment that included an ACE-inhibitor (90% vs. 58%,  $p=0.01$ ). As expected, patients with RUH had significantly higher systolic BP ( $155.6 \pm 21.6$  vs.  $137.8 \pm 16.5$  mmHg,  $p < 0.001$ ), diastolic BP ( $88.4 \pm 14.5$  vs.  $77.5 \pm 13.6$  mmHg,  $p=0.03$ ), mean arterial BP ( $115.4 \pm 17.2$  vs  $101 \pm 15.3$  mmHg,  $p=0.004$ ) and pulse pressure ( $67.3 \pm 14.2$  vs.  $60.1 \pm 12.4$  mmHg,  $p=0.001$ ). Further, RUH patients had significantly lower large artery elasticity ( $12.5 \pm 4$  vs  $14.7 \pm 3.8$  ml/mmHg $\times$ 100,  $p=0.08$ ) and lower small artery elasticity ( $4.1 \pm 2.1$  vs.  $6.9 \pm 3.6$  ml/mmHg $\times$ 100,  $p < 0.001$ ). RUH patients also had a higher systemic vascular resistance ( $1754 \pm 418.4$  vs.  $1363 \pm 371.5$  dyne $\times$ sec $\times$ cm $^{-5}$ ,  $p=0.002$ ). On CMR, RUH patients had lower right ventricular (RV) end-systolic and end-diastolic volumes ( $p=0.02$ ), as well as higher indexed left ventricular mass (LVMI) ( $61.6 \pm 17.6$  vs  $52.9 \pm 13.9$  g/m $^2$ ,  $p=0.06$ ). There were no differences in native T1, extracellular volume quantification and LGE volume fraction between RUH and RCH patients.

**Conclusions:** Patients with RUH have a greater involvement and more severe CV phenotype, that is likely to result in increased CV morbidity and mortality, including greater target end organ damage as a result of vascular adaptations and concentric remodeling.

## Keywords

Resistant uncontrolled hypertension, resistant controlled hypertension, left ventricular hypertrophy, cardiovascular remodeling, cardiovascular magnetic resonance, Africa.

## Abbreviations

ABPM	Ambulatory blood pressure measurements
ACE	Angiotensin converting enzyme
AHA	American Heart Association
ARB	Angiotensin receptor blocker
ATRH	Apparent treatment resistant hypertension
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blocker
CKD	Chronic kidney disease
CMR	Cardiovascular magnetic resonance
CO	Cardiac Output
CVD	Cardiovascular disease
CUBIC	Cape Universities Body Imaging Center
CV	Cardiovascular
DCT	Distal convoluted tubule
ECG	Electrocardiography
ECM	Extracellular matrix
ECV	Extracellular volume
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ENaC	Epithelial sodium channel
GSH	Groote Schuur Hospital

HCM	Hypertrophic cardiomyopathy
HCTZ	Hydrochlorothiazide
HFNEF	Heart failure with normal ejection fraction
HFPEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
HHD	Hypertensive heart disease
HR	Heart rate
IHD	Ischaemic heart disease
IV	Intravenous
LA	Left atrium
LGE	Late gadolinium enhancement
LV	Left ventricle/ventricular
LVDD	Left ventricular diastolic-dysfunction
LVEDD	Left ventricular end-diastolic dimension
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMi	Left ventricular mass index
MI	Myocardial infarction
MOLLI	Modified look-locker inversion recovery
MRA	Mineralocorticoid receptor antagonist
MR	Mineralocorticoid receptor

MRI	Magnetic resonance imaging
NCDs	Noncommunicable diseases
NHLS	National Health Laboratory Systems
OSA	Obstructive sleep apnoea
PVR	Peripheral vascular resistance
RAS	Renal artery stenosis
RCH	Resistant controlled hypertension
RH	Resistant hypertension
RUH	Resistant uncontrolled hypertension
ROS	Reactive oxygen species
RV	Right ventricle
RVEDV	Right ventricular end-diastolic volume
RVESV	Right ventricular end-systolic volume
ShMOLLI	Shortened modified look-locker inversion recovery
SI	Signal intensity
SR	Strain rate
SSA	Sub-saharan Africa
SSFP	Steady state free precession
STIR	Short inversion time inversion recovery
SV	Stroke volume
TOD	Target end-organ damage
TSE	Turbo spin echo
UCT	University of Cape Town

UK	United Kingdom
USA	United States of America
WHO	World Health Organization

## Chapter 1: Background and study rationale

### Introduction to hypertension

South Africa is currently experiencing a health transition that is delineated by an increase in noncommunicable diseases (NCDs), with cardiovascular disease (CVD), cancer, type 2 diabetes and hypertension being the major entities (1). The burden of NCDs in South Africa will increase substantially over the next decades if special precautions are not taken to oppose the trend (1,2).

The World Health Organization (WHO) describes hypertension (also referred to as high blood pressure – BP) as a medical condition that affects the vascular system (3). Hypertension is characterised by consistently elevated BP. The vessels are responsible for transporting blood from the heart and delivering it to organs in the rest of the body. BP is the net result of the cardiac output/stroke volume and the peripheral vascular resistance (PVR). The higher the BP, the harder the heart has to work to overcome the initial forces that oppose blood flow, and according to Laplace's law the heart adapts by hypertrophy to reduce wall stress, if BP is chronically elevated (4).

On a global scale, CVD and cardiovascular (CV) mortality are primarily attributed to hypertension, affecting over 1 billion adults globally, and resulting in 10.4 million related deaths annually (3-5). Africa is significantly affected and burdened by hypertension, with a prevalence of 30%, which contrasts with extremely low rates of awareness, treatment access and success, community education and effective management (5-6). Untreated,

chronic high BP may lead to stroke, myocardial infarction, cardiac failure, dementia, end-stage renal disease and blindness (6-10).

In sub-Saharan Africa (SSA), CVD is said to be among the top 3 causes of death and in South Africa, 210 people die daily from CVD (11), and is one of the leading causes of death in 2010, with a three-fold increase since 1990 (12). During this period, hypertension has caused over 500,000 deaths and a loss of 10 million life-adjusted years (12). Hypertension was also among the top 10 leading risk factors for disability, contributing more than 11 million years of life lost to disability by hypertension (12). Hypertension contributes to CVD (with half of CVD attributable to hypertension in SSA), including stroke and heart failure. Elevated BP has yielded over 40% of deaths in diabetic patients and about 13% of deaths generally (12).

Hypertension is one of the major, yet adjustable risk factors for CVD (13) and has also been identified as the leading risk factor for mortality (14-15). In black South Africans, the clinical presentation of hypertension is severe and difficult to treat compared to white South Africans and citizens from developed countries (16). In addition, the young population of black South Africans is likely to present with severe and uncontrolled hypertension (13,16-17).

### Classification and staging of hypertension

There are many definitions and risk criteria that exist to characterise and stratify hypertension, with the common definition being a BP that is  $\geq 140/90$  mmHg. However, CV risk is said to increase progressively from BP levels as low as 115/75 mmHg and upward, with a two-fold increase in the likelihood of both coronary heart disease and stroke for

every 20/10mmHg increment of BP (18). Figure 1.1 shows the several types of hypertension and how they are classified. These are known as resistant uncontrolled hypertension (RUH), resistant controlled hypertension (RCH) and controlled hypertension, respectively, with refractory and resistant hypertension (RH) used interchangeably. (Figure 1.1)

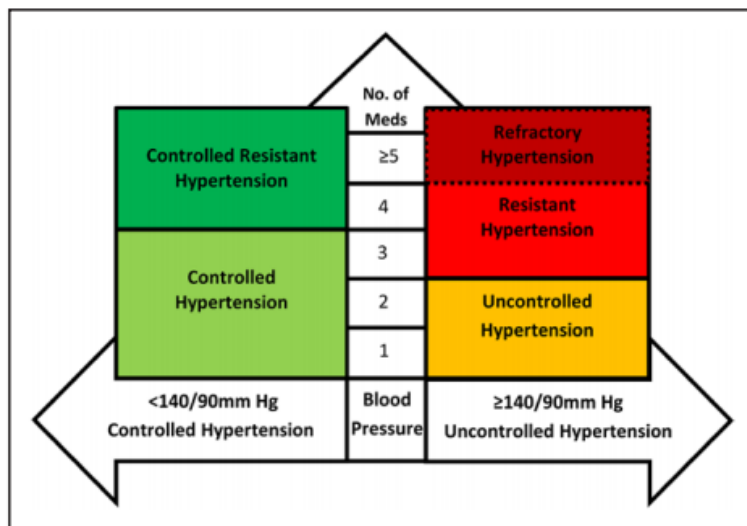


Figure 1.1: Hypertension classification based on blood pressure control and number of antihypertensive medications. (Dudonbostel T, Siddiqui M, Oparil S. Refractory Hypertension: A novel phenotype of antihypertensive treatment failure. *Hypertension*. 2016;67 1085-1092.)

### Resistant Hypertension

RUH is marked by elevated BP that remains high ( $\geq 140/90$  mm Hg) despite the concurrent use of effective doses of 3 or more antihypertensive agents from different treatment regimens, including a long-acting calcium channel blocker (CCB), an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and a diuretic (19). Patients whose BP is controlled via the use of 4 or more different classes of medications are considered resistant to treatment and classified as RCH (19). The American Heart Association (AHA) amended the definition of RH in 2008 to include RCH patients (20). RH should include patients who fail to control BP in tandem with poor adherence and an inadequate treatment regimen, including those with true treatment resistance. A more

accurate and often used term to cover both true resistance and poor adherence is referred to as apparent treatment resistant hypertension (ATRH) (20).

According to a study by Acelajado *et al* (21), a small percentage of patients with RH who never achieve BP control despite maximal medical treatment, represent a potentially novel and distinctive phenotype which is different from the larger proportion of patients whose BP can be controlled. These patients are said to have RUH. The classification of RH exists to identify patients who are at an increased risk for CV mortality and morbidity. Often patients with RH present with secondary causes of hypertension and may suffer from adverse effects such as target end-organ damage (22).

### Pathophysiology and aetiology of hypertension

RH is thought to be of renal aetiology, hallmarked by excessive fluid retention as a result of obesity, chronic kidney disease (CKD), age, hyperaldosteronism, black race and a high dietary salt intake (21,23). This pathophysiological proposal is supported by the role that diuretic therapy intensification plays in effectively achieving BP control in patients with RH (24-25). In a study by Rayner *et al*, 20% of the Khoi San had a polymorphism of the epithelial sodium channels (ENaC) in renal tubules. This genetic mutation allows the Khoi to retain sodium and water while simultaneously losing potassium (26-27). This adaptive mutation would have been beneficial to the Khoi residing in the Kalahari Desert. However, due to changes brought about by migration and industrialisation with increased salt and reduced potassium intake, this adaptation has become a double-edged sword, posing more harm than good (28). Genetic variants of the ENaC are responsible for about 6% of hypertension

in black South Africans via the R563Q variant and 5% in black Africans of Caribbean/North African origin residing in London, United Kingdom (UK) via the T594M variant (28-29).

Hyperaldosteronism has been closely associated with the development of hypertension, resistant or otherwise (21). Aldosterone is produced by the zona glomerulosa cells in the kidneys, and modulates the mineralocorticoid pathway by binding to the mineralocorticoid receptors in the epithelial cells of the distal convoluted tubule (DCT) and collecting duct of the nephrons (30-32). Aldosterone promotes water and sodium reabsorption and potassium secretion by regulating the sodium-potassium exchange pump (30,32). Primary aldosteronism marked by aldosterone excess, low plasma renin activity and treatment resistance in hypertension best illustrates the role of aldosterone in RH (32). Hyperaldosteronism is common, accounting for 20% of the RH population (19). Supporting evidence of the role of excess aldosterone levels in RH is further illustrated by the efficacy of aldosterone antagonists in lowering BP (33).

Other secondary causes of RH include comorbidities like obstructive sleep apnoea (OSA), chronic kidney disease (CKD), pheochromocytoma, and renal artery stenosis (RAS); lifestyle factors such as obesity, high dietary salt intake, and heavy alcohol consumption; drug related causes including oral contraception and use of non-narcotic analgesics and lastly, pseudoresistance which includes poor adherence to medical therapy, white-coat hypertension and inaccurate BP measurement (19,34).

## Prevalence of resistant hypertension

The prevalence of RH across the SSA is not well documented, however, a few studies have conducted analyses across several parts of Africa to determine the rate of risk. Noubiap *et al* (35) conducted the first ever meta-analysis to measure the global prevalence of RH and reported SSA to have the lowest rate of RH of 10.1% in the WHO regions, compared to the Western Pacific with the highest rate of 19.2% (35). The prevalence of RH extends anywhere from 8.4% to 17.4% across American and European countries (1,36-38).

Several observational studies outside Africa have defined patients with RH, and report the prevalence of RH at approximately 10-15% of treated hypertensive patients (37). For example, in a cross-sectional analysis of >470,000 individuals, 60,327 had RH, representing 12.8% of all hypertensive individuals and 15.3% of those taking antihypertensive medications (37).

#### Risk factors and associated comorbidities in resistant hypertension

Several studies have reported on patient characteristics associated with RH. In an analysis of the Framingham study, old age was the strongest risk factor associated with failure to adequately control BP (39). Second to old age, left ventricular hypertrophy (LVH) and obesity were the strongest predictors of lack of systolic BP control (39). When compared with individuals who presented with controlled BP (<140/90 mm Hg) with 1 or 2 medications, individuals with RH were older, obese, and more likely African American and female, and had a greater prevalence of comorbidities, including diabetes, ischaemic heart disease (IHD), cerebrovascular disease, and CKD (Table 1.1) (19). Finally, the strongest predictor of treatment resistance was having CKD as defined by a serum creatinine of 1.5 mg/dL or greater (19,39-40).

---

**Table 1.1: Patient characteristics associated with resistant hypertension**

**Older age**

**High baseline blood pressure**

**Obesity**

**Excessive dietary salt ingestion**

**Chronic kidney disease**

**Diabetes**

**Left ventricular hypertrophy**

**Black race**

**Hyperaldosteronism**

---

### Prognosis of resistant hypertension

Calhoun *et al* stated that the prognosis of RH compared to controlled hypertension had not been fully elucidated (41). Recent studies have clearly shown the likelihood of CV injury, renal impairment and all-cause mortality as a result of suffering from RH. A study by Daugherty *et al* was the first to determine the prognosis of RH by conducting a longitudinal assessment of a large cohort of subjects with rigorously defined RH (42). Their study analysed longitudinal data collected over a period of 5 years, and demonstrated that compared to controlled hypertensives on 3 medications, patients diagnosed with RH had a poorer prognosis, likely due to target end-organ damage such as the development of CKD (42). Interestingly, both groups of patients (controlled and RH) had similar durations of hypertension (all patients with incidental hypertension during the analysis period were included) however, the prognosis of RH remained worse compared to controlled

hypertension, suggesting that the duration of hypertension alone, might not be sufficient to explain the poor CV prognosis in RH.

Excess aldosterone levels found in patients with RH has been proposed as one of the main contributing factors to CV mortality (22). Individuals diagnosed with primary hyperaldosteronism have been demonstrated to experience higher rates of CV events and target end organ damage (TOD) (33). In a separate study involving over 400, 000 patients, compared with the controlled hypertension group, patients with RH had a 32% increased risk of developing end-stage CKD, a 24% increased risk of an IHD event, a 46% increased risk of heart failure, a 14% increased risk of stroke, and a 6% increased risk of CV death (43).

#### Treatment for resistant hypertension

Treatment of RH relies heavily on intensified diuretic therapy (use of a long-acting thiazide diuretic), combination therapy (combining 2 agents of different classes) and the use of a mineralocorticoid receptor antagonist (MRA) such as spironolactone. This treatment regimen has been shown to have a significant effect on lowering BP in resistant hypertension(19). (Table 1.2)

Diuretics e.g hydrochlorothiazide
Combination therapy
Mineralocorticoid receptor antagonist e.g spironolactone
ACE Inhibitor/ Angiotensin receptor blocker

## Rationale for this study

A small percentage of patients with RH who never achieve BP control despite maximal medical treatment represent a potentially novel and distinctive phenotype which is different from the large proportion of patients with RH whose BP can be controlled. The impact that RH has on the hypertension epidemic worldwide is striking. The burden of hypertension in SSA is likely to increase, it is for this reason, that identifying and categorising such patients is important in understanding the mechanisms of treatment resistance in this phenotype. Our study hopes to define the phenotype and imaging characteristics of resistant uncontrolled and resistant controlled hypertension in patients using CMR. Our findings may contribute to improved understanding of the pathophysiology of this disease in the African population and may point to a need for development of more effective treatment suited individual genotypes within this population.

## Study aims

The aim of this study was to identify patients with resistant uncontrolled hypertension (RUH) and compare phenotypes in these patients to resistant controlled hypertensives (RCH), using a combination of electrocardiography (ECG), echocardiography, applanation tonometry and cardiovascular magnetic resonance (CMR).

## Chapter 2: Literature Review (Cardiovascular adaptation to hypertension)

### Introduction

Among patients with resistant hypertension (RH), a proportion present with blood pressure (BP) that remains elevated despite long-term use of maximal medical therapy. The prevalence of RH in South Africa is currently unknown, however, clinical reports suggest that it is not rare. Patients with RH are more likely to develop complications such as CKD, LVH, retinopathy, heart failure, coronary artery disease, stroke, vascular dementia, peripheral arterial disease and obstructive sleep apnoea (44-47). This literature review explores the current available evidence on ventricular remodeling in RH as well as the use of CMR in the diagnosis and evaluation of hypertension.

### Functional and structural adaptations associated with hypertension in the cardiovascular system

Severe uncontrolled hypertension affects vital organs such as the heart, brain, kidneys, eyes and vessels through vascular complications, as a result of persistent elevated BP and loss of tissue compliance (48-49). Pertaining to the CV system, the presence of LVH, myocardial fibrosis, diastolic and systolic ventricular dysfunction, heart failure, atrial myopathy and atrial fibrillation are manifestations that define the phenotype of hypertensive heart disease (HHD) (48-49). Regarding the vascular system, the major findings include impaired endothelial function, remodeling of the small and large arteries with impaired vasodilation, impaired distensibility and pulse wave velocity, and atherosclerotic vascular disease marked by the development of stenoses and aneurysms. CMR is the gold standard for imaging of the ventricles and vasculature due to its unique ability to visualise and assess structural and functional changes in hypertensive patients, leading to an accurate diagnosis (48).

### *Left ventricular hypertrophy in hypertension*

One of the pathological biomarkers in HHD is the thickening of the left ventricular (LV) wall as a physiological response to minimise wallstress in the presence of elevated BP. Following a stable compensation by the LV, decompensation occurs, (“transition to heart failure”), leading to dilatation of the LV, with a normal ejection fraction (EF) or a reduced EF. Hypertension is one of the leading risk factors for heart failure, with more than a 50% chance of developing heart failure with preserved EF (HFpEF) (discussed later under “diastolic dysfunction”) versus heart failure with reduced ejection fraction (HFrEF) (49-50).

An increase in LV mass is the *sine qua non* of LVH, and this increase in mass is confirmed by measurements of post-mortem weight, electrocardiographic (ECG) criteria, and by cardiac ultrasound or CMR. Early echocardiographic studies by Devereux and Reichek defined LVH as LV mass that exceeds 250g (51). This increase in LV mass is not only unique to hypertension; some disease states such as aortic stenosis, hypertrophic cardiomyopathy (HCM), infiltrative myocardial diseases (amyloid, sarcoidosis, and Fabry’s disease), as well as athlete’s heart and pregnancy, may mimic LVH associated with hypertension. However, CMR is exceptional in evaluating a differential diagnosis by assessing the pattern of LVH, presence of enhancement and pattern of fibrosis (52). Recently, gender-based values in the detection of LVH have been calibrated for age and body surface area and published, using CMR as the preferred and recommended technique (53).

Anatomical and physiological adaptations that occur in patients with hypertensive LVH include cardiomyocyte hypertrophy, accumulation of the extracellular matrix (ECM)

constituents (54-55), with accelerated deposition of collagen and fibronectin, and impaired vasculature of the intramyocardial coronary vasculature, including medial hypertrophy and perivascular fibrosis (56). The aetiology underlying “progression to hypertrophy” includes more than a compensatory response to the altered shear stress from elevated BP, it also encompasses the influence of neurohormones (57), growth factors, and cytokines (49).

A direct link exists between adverse CV outcomes and LV mass (58). There is ample evidence that reversing the cycle of LVH, leads to diminished risk of mortality. Simply put, regression of LV mass as a result of antihypertensive treatment confers a low risk of stroke, acute myocardial infarction, heart failure, and all-cause mortality (59). The typical paradigm and development of LVH can be implicated in the progression of HHD and its direct relationship to heart failure has been under the spotlight in recent years. Many pathological changes are present in patients with hypertensive LVH including cardiomyocyte hypertrophy and increased amounts of interstitial and perivascular fibrosis (54).

LVH has three anatomical models initially reported by Ganau *et al*, namely concentric hypertrophy, eccentric hypertrophy and concentric remodeling (60). Concentric LVH is defined by an increase in LV mass, increased global LV wall thickening in response to pressure overload and a normal LV cavity size. Concentric LVH is prevalent in middle-aged and elderly patients and is closely linked to increased cardiac output. Concentric remodeling is a result of long-standing hypertension and is usually marked by normal LV mass, normal LV cavity size and increased LV wall thickness. Eccentric hypertrophy is characterised by normal global LV wall thickness and an increase in LV mass by chamber dilatation. Conversely, it is

frequently seen in the younger population and is associated with decreased cardiac output (61).

The rationale for developing a specific LV pattern in response to hypertension across the patient population is unclear, but features such as pressure overload, volume overload, ethnicity, gender, age, obesity, and plasma renin levels are all reported to have influence (49). Further, there is a lack of understanding and knowledge surrounding the different LVH patterns and how they affect the prognosis of hypertension.

#### *CMR for left ventricular hypertrophy*

CMR has the ability to not only quantify LV mass, volumes and ejection fraction, but it can also assess the pattern of hypertrophy (also referred to as the LV geometry), which may or may not have prognostic importance. CMR is the reference method for imaging LV function, due to its high accuracy and reproducibility (62). The relative wall mass can be calculated by dividing the LV mass by the LV end-diastolic volume (LVEDV), and effectively indexes ventricular wall thickness to cavity size. Both patterns of LVH are established risk factors for CVD, however concentric hypertrophy has repeatedly been shown to be the culprit which confers a markedly increased risk (63).

Despite the different patterns of LVH and their association to CVD, regression of LVH has been shown to lower this risk (64). CMR been used as a tool for analysing ventricular mass reduction following LVH in several intervention studies in hypertension. The LIFE sub-study, which evaluated the relationship between high BP and ventricular remodeling (65); and the TELMAR study which assessed the outcome of using telmisartan compared to metoprolol to

treat LVH in patients with uncontrolled hypertension (66); the LVH-4E, where LVH regression was monitored by studying the effects of eplerenone compared to enalapril or a combination of both in hypertensive patients (67); the ALIVE study, in which benazepril with either amlodipine or a diuretic was tested (68); and the ALLAY trial, that proved the unmatched effectiveness of aliskiren in LVH regression, and its similar potency to losartan in reducing LV mass (69); all confirmed the CV benefits of reducing LVH.

The pathological and anatomical patterns of LVH are a hallmark of many disease processes in overlapping cardiomyopathies, therefore determining the aetiology of LVH is often a common and challenging clinical problem. Some cardiomyopathies and conditions can imitate LVH, these include cardiac sarcoidosis, Fabry's disease, infiltrative diseases, aortic stenosis, athlete's heart or exercise-induced ventricular hypertrophy, pregnancy and hypertrophic cardiomyopathy (HCM). CMR has a distinctive ability to noninvasively characterise myocardial tissue and can provide detailed information on ventricular structure and function, pattern of late gadolinium enhancement (LGE), and valvular function. With regards to infiltrative diseases, a unique and specified pattern of LGE has been described for amyloidosis (70,71). with 80% sensitivity, specificity of 94% and positive predictive value of 92% that has simplified the differential diagnosis. Similarly, haemochromatosis, iron overload cardiomyopathy and Fabry's disease have fairly pathognomonic features on parametric mapping with CMR (71).

Recently, multiparametric CMR was used to differentiate HCM from hypertensive LVH and unique hypertrophic phenotypes were noticeable (72). The hypertensive patients presented with increased LV wall stress, reduced EF, reduced anteroseptal systolic strain, and

increased cardiac chamber volumes, while patients with HCM had supranormal EF, reduced LV wall stress, decreased longitudinal systolic strain and fibrosis. Logistic regression analysis identified increased LV wall stress as the main biomarker of hypertension while HCM was best characterised by reduced total global longitudinal strain.

Exercise-induced ventricular hypertrophy also known as athlete's heart, can be identified from other types of pathological hypertrophy with CMR-derived diastolic wall-to-volume ratio (73,74). A cut-off value of less than  $0.15 \text{ mm} \times \text{m}^2 / \text{ml}$ , is said to have a 99% specificity for sport related LVH. However, this finding requires further validation and confirmation in larger cohorts.

CMR is an attractive imaging technique because it provides highly reliable, precise and reproducible measurements of LV function and mass, and it allows thorough myocardial fibrosis analysis. It is the most reliable technique of identifying hypertension related LVH from other CV causes, and can also be used to screen for secondary causes of systemic hypertension.

#### *Right ventricular dysfunction in hypertension*

Changes in the LV in response to workload and pressure overload have been well documented, whereas the right ventricle (RV) remains relatively understudied. Previous studies have demonstrated the link between arterial hypertension and RV remodeling (74). Newer studies have investigated the RV mechanics in hypertensive patients and have illustrated a significant deterioration of RV longitudinal deformation and the association

between RV longitudinal strain and functional capacity. These studies have revealed that RV longitudinal strain is a strong predictor of RV dysfunction (75).

Three possible mechanisms underlying RV hypertrophy have been established: (1) overstimulation of the autonomic nervous system and the renin-angiotensin-aldosterone system often leads to decreased arteriolar compliance which results in increased RV wall thickness (76); (2) ventricular interdependence via the interventricular septum; and (3) reactive oxygen species (ROS) and impaired endothelial function can lead to changes in the pulmonary circulation that ultimately lead to RV hypertrophy (77).

Several studies have documented ventricular interdependence in HHD, using echocardiography and CMR. Because the heart functions as a single unit, structural and functional changes that occur in the LV, also affect the RV (78). Ventricular interdependence involves force that is transmitted from one ventricle to the adjacent one, through the myocardium and interventricular septum. This mechanism occurs independently from hormonal, circulatory or neural control. About 20%-40% of the per beat RV systolic function and volume is dependent on LV contraction (79). Ventricular interdependence occurs mainly due to the ventricles close anatomic association: sharing common muscle fibers and a septal wall. In a study by Todiere and colleagues, 25 patients with uncomplicated, mild to moderate essential hypertension were compared to 24 healthy age- and sex-matched controls using CMR. The authors reported that RV mass index (RVMI), ventricular wall thickness and remodeling index were greater in hypertensive participants and associated with reduced peak filling rate. They also showed that systemic hypertension leads to RV remodeling and impaired diastolic function (80,81).

In a study by Ilieva *et al*, spontaneously hypertensive rats (SHR) were used to investigate the development of cardiac hypertrophy in response to systemic hypertension in both ventricles and demonstrated the involvement of the RV. They reported structural adaptations that occur in the LV and to a lesser degree in the RV, and these included cardiomyocytic hypertrophy, hypertrophy and hyperplasia of cardiomyocytic nuclei, focal myocytolysis and increased collagen deposition in the interstitial space. They also reported a unique finding, which was the presence of mast cells in the interstitium of the RV (81). Although mast cells play a role in mediating ECM degradation and synthesis (82), they are also implicated in fibrotic remodeling of the heart due to hypertension and myocarditis (83).

#### *CMR for right ventricular dysfunction*

RV function can be assessed using either echocardiography or CMR, however due to the anatomy of the RV in relation to the LV, imaging the RV may prove a challenge on echocardiography. Thus CMR automatically becomes the preferred method, due to its ability to acquire parallel and contiguous tomographic images, in any orthogonal plane, with high temporal resolution, and for providing accurate volumetric quantification of size and function. CMR has better contrast between blood and myocardium as well as epicardium and surrounding fat (80,84). CMR accurately assesses volumetric, mass, and quantitative functional analysis of the LV and RV. CMR also allows regional assessment of the entire circumference of the LV and RV in each slice (septum, anterior, lateral, and inferior walls of the LV) and free wall of the RV. The RV free wall is best visualised on standard transaxial cine images, as it lies approximately parallel to the anterior chest wall, and both long axis contraction and fine detail of regional function can be assessed. Horizontal long axis and RV

vertical long axis views can be used to assess RV function. The motion of the interventricular septum, which is best visualised in a short axis stack cine image, can be helpful in diagnosing RV volume and pressure overload (52). However, CMR is expensive compared to other imaging tools such as echocardiography, and is not available in many parts of the world. This could explain, in part, why RV involvement in cardiac diseases lacks data and further elucidation.

### *Myocardial fibrosis in hypertension*

The ECM of the heart, is a dynamic environment that is composed of fibrillar collagen, which is important for maintaining the optimum structure and plasticity of cardiomyocytes, fibroblasts, and vascular cells in the heart. In the diseased state of the heart, the ECM is subjected to changes in the structure of the cells as well as subcellular changes that continuously influence normal cardiac physiology (85). Impaired structure and function of cardiomyocytes has always been a focal point of CV injury, however, it is now known that changes in the cardiac ECM and cardiac remodeling are associated with the development and progression of CVD leading to heart failure (85). The modifications in the ECM activate the pathways of cardiac fibrosis. Acute scar tissue formation occurs at the site of cardiac injury due to myocardial infarction to provide myocardial healing and prevent rupture or tethering of the myocardium (86). On the extreme end of the continuum, persistent and widespread or localised reactive myocardial fibrosis is a result of either pressure or volume overload due to long-standing hypertension, metabolic disorders, valvular heart diseases, ischaemic insults on the heart (in areas remote from the infarction), or diffuse myocardial diseases, such as cardiomyopathies (87). Such scarring distorts the myocardium's normal physiology by directly altering its contractile abilities.

Increased collagen production is a hallmark of myocardial fibrosis. Collagen production occurs at an accelerated rate compared to collagen degradation (which may either decrease or remain unchanged) (88,89), and accelerated diffuse collagen deposition in the interstitial and perivascular spaces (90). The dysregulation of specific pro- and antifibrotic factors, including cytokines and chemokines, growth factors, proteases, hormones, and ROS, are responsible for the alteration of the collagen matrix (91). This dysregulation of collagen turnover takes place mainly in phenotypically transformed fibroblasts, termed myofibroblasts (85,92). Myocardial fibrosis disrupts the myocardial structure and make-up, contributes to myocardial disarray, and determines mechanical (93,94), electrical (95-97), and vasomotor dysfunction (98), thus promoting the progression of cardiac diseases to heart failure (99).

Myocardial fibrosis is associated with decreased ventricular compliance, LV systolic dysfunction and development of diastolic dysfunction (54). The degree of this fibrosis as measured by LGE-enhanced CMR has been proven to have a direct correlation to the presence of diastolic dysfunction in patients with hypertension (51,54).

### *CMR for myocardial fibrosis*

Basic scientific research using animal models, as well as clinical studies have shown that hypertensive LVH is defined by accumulation of type I and III collagen fibers in the interventricular septum and in the LV free wall (100). This increase in collagen content appears to be a typical characteristic of LVH, regardless of its cause and severity of LV remodeling (101). Myocardial fibrosis can be localised to one area, also referred to

as reparative or replacement fibrosis (102), or it can be widespread, also known as interstitial fibrosis, the most frequently occurring pattern in HHD (103). Fibrosis leads to myocardial stiffness and subsequent changes in ventricular function, electrophysiology and myocardial perfusion that may potentially affect prognosis (103).

LGE-CMR has the ability to detect reparative myocardial fibrosis, as shown in several CVDs including hypertension (101,104-107). The pattern of fibrosis in HHD is often wide-spread and is therefore undetected via LGE-CMR: this becomes a major limitation of LGE-CMR. LGE-CMR is unable to detect diffuse myocardial fibrosis because LGE depends on relative differences in signal intensities and uses the myocardium with the lowest signal intensity as a reference for normal or healthy myocardium, irrespective of the extent of fibrosis established within. To detect the diffuse fibrotic pattern, the T1 mapping sequences should be employed. T1 maps are superior over LGE-CMR as they are based on pixel-wise measurement of the longitudinal relaxation time. Each tissue exhibits a characteristic T1 relaxation time at a selected magnetic field strength that depends on tissue composition which can be shown as a colour-coded map. Thus, deviation from normal ranges could be used to detect and quantify pathological processes such as hypertensive diffuse myocardial fibrosis (48).

The Modified Look-Locker Inversion recovery (MOLLI) is a pulse sequence that allows for the quantification and mapping of T1 values in the myocardium. MOLLI is different from the traditional Look and Locker sequence in two ways: (1) it can acquire specific data at any point in time of the cardiac cycle; and (2) it is able to combine images from three consecutive inversion-recovery Look-Locker experiments into one data set, producing

single-breath hold single-slice T1 maps of the myocardium (108-110). A newer sequence known as the Shortened Modified Look-Locker Inversion recovery (ShMOLLI) (111) has also been established and tested (112). It is a shortened version of the MOLLI and it can produce well-defined myocardial T1 maps by using sequential inversion recovery measurements within a single shortened breath-hold. Both methods have been proven as promising sequences for the detection of interstitial myocardial fibrosis in patients with HHD.

#### *Diastolic dysfunction in hypertension*

Diastole is the phase of the cardiac cycle encompassed by ventricular relaxation, and comprises 3 sub-phases of filling (rapid filling, diastasis, and atrial contraction). Diastolic dysfunction refers to abnormal relaxation patterns of the ventricles; these patterns include slow or delayed relaxation, stiffness of the LV during diastole, and altered filling patterns of the ventricles (113,114). In the presence of LVH, change in LV geometry and myocardial fibrosis, the LV begins to experience abnormalities of the diastolic pattern in tandem with the above-mentioned adaptations. These impairments in diastolic function of the LV are referred to as LV diastolic dysfunction(LVDD) which is characterised by the inability of the LV to fill with sufficient blood at low pressures, thus delaying chamber filling, which results in incomplete LV filling in the absence of increased left atrial (LA) pressure. Thus, LV filling becomes more dependent on LA contraction and higher atrial pressures (115).

General or global abnormal relaxation may be a consequence of any mechanistic action that results in a cytosolic calcium deficit and the actin–myosin cross-bridge detachment (116), whereas increased LV chamber stiffness (reduced LV compliance or distensibility) results from alterations of the myocardial composition, including interstitial fibrosis,

alterations in the phosphorylation of titin, and accelerated microtubule growth in the cardiomyocytes (114,117).

LVDD is characterised by changes in LV diastolic filling, which may include impaired myocardial relaxation and reduced compliance of the myocardium (113,114). It is prevalent in the older community and is a strong hallmark of CV insults and incident heart failure (114). The following risk factors: diabetes mellitus, hypertension, obesity and coronary artery disease, are implicated in the development of LVDD (118). Hypertension remains the strongest predictor for the development of LVDD in the population and an important cause of heart failure (118,119). Importantly, LVDD is considered to play a critical role in the progression of hypertension to heart failure, specifically in individuals with HFpEF (119).

Ambulatory BP measurements (ABPM), are highly favoured due to their more illustrative methods of haemodynamic pressure and shear stress imposed by hypertension, and their stronger association with LVDD than casual BP measurements (120). The use of ABPM is useful in identifying individuals with masked hypertension, who suffer the same risk of developing LVDD, to those with long-standing hypertension (121).

#### *CMR in the assessment of diastolic dysfunction*

Diastolic function can be assessed noninvasively using echocardiography, mainly via flow Doppler and tissue Doppler imaging. Using CMR to assess diastolic function requires employing high temporal resolution sequences (122). Therefore, it becomes crucial to adopt several imaging techniques, such as retrospective gating, which allows quantification of the change in ventricular volume at various time points in the cardiac cycle, and provides

parameters such as atrial filling ratios, peak diastolic filling rate and time to peak filling rate (122). Further, analysis of 3D myocardial strains with tissue tagging gated to diastole, and mitral inflow velocity curves obtained with phase contrast sequences are useful for the study of diastolic function with CMR (122). A new CMR-derived index: diastolic volume recovery, calculated as the segment of diastole required for recovery of 80% stroke volume, has been recently shown to provide the best performance in detecting LVDD compared to echocardiography (122).

### *Vascular adaptations in hypertension*

Blood vessels, vascular systems and their networks, as well as the endothelial cells, are dynamic constituents of the CV system, with adaptation properties in response to a change in their internal environment, through haemodynamic, hormonal, cytokine and metabolic stimuli. These modifications or adaptations include alterations in vessel density, vessel wall thickness, smooth muscle tone and vessel diameter. Initially, an increase in BP, due to an increase in cardiac output, leads to vasoconstriction, which prospectively results in reduction of vessel diameters via wall remodeling. Secondly, rarefaction of microvessels and capillaries results in increased reduction of the total peripheral vascular cross-section area. Due to structural autoregulation, an increase in BP and peripheral resistance perpetuates the elevated BP above the level generated by the initial increase of cardiac output. Recent evidence suggests that vascular adaptation in capillaries and venules appears to be pathognomonic in hypertension (122,123).

Microvascular networks which include terminal arterioles, metarterioles, capillaries and venules are versatile microvessels, highly capable of repeatedly adapting to internal

impulses. Haemodynamic stimuli including haemodynamic load (wall shear stress) and BP (circumferential wall stress) as well as metabolic factors (e.g., oxygen partial pressure or related metabolic signals) are primary examples of such impulses (124).

Vascular modifications occur at different time points and involve vascular tonicity, the architectural make-up of the vessel wall, and the vessel density. Vascular tone controls some of the earliest responses and may prompt changes of vessel diameter within seconds. An overstimulated vascular tone due to persistent changes in the internal environment (125), leads to vascular remodelling (126). Vascular remodeling can be classified according to observed changes in vessel diameter and wall thickness and/or wall mass. Diameter increase, and decrease is referred to as “outward” and “inward” remodeling (127).

If cardiac output remains permanently elevated by whatever mechanism, an increase in vascular tone is observed (126,127), and pruning, evident from vascular rarefaction, is also observed (128,129). This results in a lack of sufficient blood supply and an increase in peripheral flow resistance which further increases BP via a positive feedback loop. This phenomenon has been called structural autoregulation (130,131). Based on the above, it is evident that structural autoregulation is not only a vicious cycle that perpetuates haemodynamic impairments, but its alterations in vascular adaptation to pressure, or endothelial function, result in hypertension (131). The increased peripheral resistance and its constituents, i.e., tone of vascular smooth muscle cells, inward remodeling, and rarefaction, are more likely to lead to deficits in oxygen and nutrient supply (130,131).

*CMR in the assessment of aortic and peripheral vascular disease*

Systemic hypertension has been identified as one of the leading risk factors for aortic and peripheral vascular disease (132). Conversely, the association between CV risk factors including hypertension (103,133,134) and atheromatous plaques in the aorta, as well as their potential to be used as prognostic biomarkers (135), has been documented. CMR has the ability to not only provide an extensive assessment of the aortic anatomy and physiology, but it can also assess aortic structure and function in diseased states by including not only the assessment and follow-up of aortic wall syndromes, but also valuation and measurement of the atherosclerotic plaque volume, composition, biological activity, and quantification of aortic functional parameters such as compliance, distensibility and pulse wave velocity (136).

Using CMR as a tool for plaque imaging may be an important step in identifying the extent of risk, which may affect the approach to treatment, and may be useful in plaque-regression studies. It has been shown that patients with a history of detrimental CV events are at a higher risk for developing malignant plaque formation (136). Similarly, the presence of aortic atheroma in a particular patient indicates a greater likelihood for a CV event than could be expected from the Framingham score alone, which was not designed to detect atherosclerotic plaques (137). Black blood CMR imaging has a high accuracy and reproducibility rate for assessment and volumetric quantification of atheroma plaques in the carotid arteries (138) and aorta (139,140-142).

CMR flow imaging and cine sequences provide the advantage of performing a functional assessment of the aorta. Haemodynamic load affects arterial remodeling and often leads to arterial stiffness, both early manifestations of adverse anatomical and physiological

modifications within the vascularwall (138). Additionally, atherosclerosis, as well as endothelial function, depends on arterial wall shear stress. Flow-sensitive 4D-MRI, which allows the depiction of a 3D model of the aorta and quantification of multi-directional blood flow *in vivo* as well as the acquisition of time-resolved blood flow velocities in three directions, provides information regarding the regional differences in absolute wall shear stress and oscillatory shear index. Such a sequence has the potential to explain the pathophysiology of atherosclerotic lesions and how their locations correlate to cardiovascular mortality (143).

### *Conclusion*

Advances in CMR techniques over the years have provided novel insights into the morphological and pathophysiological adaptations associated with HHD, proving yet again, that CMR is ideal for cardiovascular adaptations to hypertension. CMR is likely to extend our understanding of CV phenotypes in RH patients.

## Chapter 3: Methods

### Study Aim and Design

This study was a cross sectional case-control analysis of patients with resistant uncontrolled hypertension (RUH) and how their phenotype compares to patients with resistant controlled hypertension (RCH).

### Study Population

This study included adult patients with RUH and patients with RCH.

### Inclusion Criteria

- Patients with RH were included in the study attending the Hypertension Clinic at Groote Schuur Hospital.
- Informed consent and willingness to undergo CMR.

### Exclusion Criteria

- Patients with an estimated glomerular filtration rate (eGFR) of <30ml/min based on the Modification of Diet in Renal Disease (MDRD) calculation.
- Patients with white-coat hypertension or poor treatment adherence.
- Inability to tolerate CMR or contraindications to MRI.
- Pregnant or lactating patients.

### Recruitment and enrolment

Patients whose BP remained above goal (140/90mmHg) despite 3 or more antihypertensive medication were defined as RUH. Patients whose BP was adequately controlled via the use

of 4 and more antihypertensive medication were defined as having RCH (<140/<90mmHg). An amlodipine assay was used to assess patients' level of adherence to the antihypertensive medication, and latest eGFR results were obtained from patients' National Health Laboratory System (NHLS) records to assess kidney function. Figure 1.2 shows patient recruitment and enrollment:

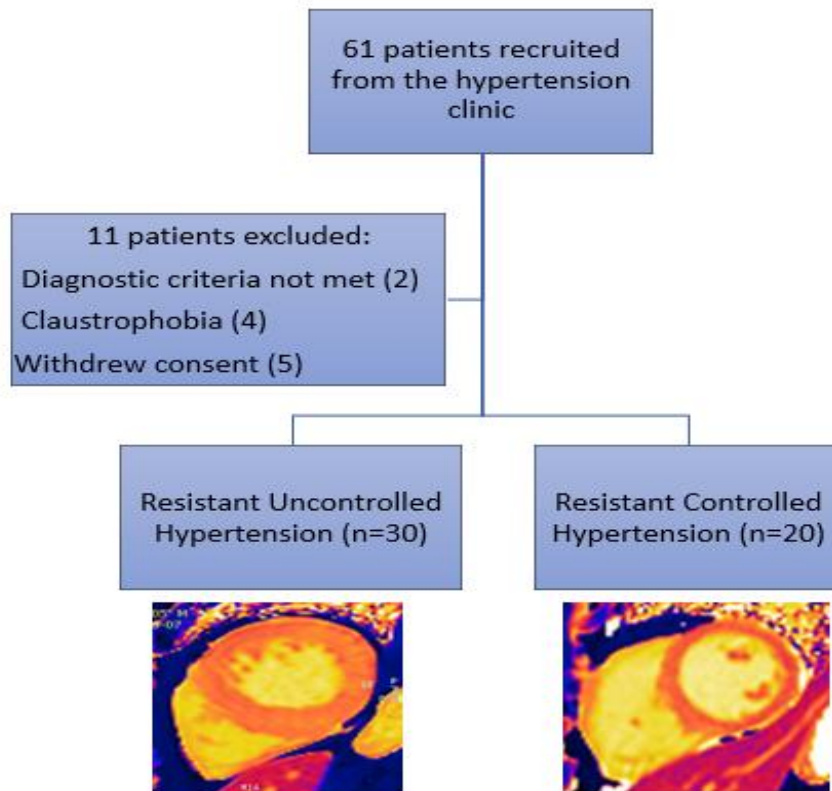


Figure 1.2 Study size and exclusion criteria.

## Research procedures and data collection methods

### Blood Pressure Recording

BP in the clinic was measured by two trained professionals using an automated BP machine (Dinamap Carescape Monitor (Woodley Equipment Company Ltd) in a seated patient with the arm properly supported and use of a correct cuff size. Baseline BP values were recorded

before and after administration of medical therapy. The mean of the last 3 readings was used for determining BP control.

### CMR Imaging

CMR imaging was conducted at UCT Cape Universities Body Imaging Centre (CUBIC) and patient folders were obtained from the Groote Schuur Hospital Hypertension Clinic. Data from the patients' CMR reports were processed into an electronic database and analysed using IBM SPSS, version 25 (IBM, Somers, New York, USA). CMR studies were reported according to a standardised protocol. The following cardiac parameters were documented:

- a. LV and RV volumes, mass and function.
- b. Myocardial tissue characterisation using dual inversion recovery T2-weighted imaging and T1-weighted imaging.
- c. Velocity-encoded 2-D phase contrast (flow) imaging.
- d. Strain imaging
- e. Native T1 and T2 mapping
- f. Late gadolinium enhancement (LGE) imaging for viability and focal fibrosis assessment.
- g. Postcontrast T1 mapping and ECV estimation

### CMR Analysis

Circle CVI<sup>42</sup> software (Circle Cardiovascular Imaging Inc, Calgary, Canada) was used to perform post processing and post scan analysis of the following CMR image parameters:

**Cine images:** Left atrium (LA), right atrium (RA) size and LA area. Left ventricular end diastolic dimension (LVEDD) was measured using free-hand contouring. Ventricular ejection

fraction (LV and RV) were analysed by manually contouring the epicardial and endocardial borders of the LV and endocardial borders of the RV in the SA stack at end-systole and end-diastole. RV and LV end-diastolic and end-systolic volumes were used to calculate stroke volume and ejection fraction. Myocardial mass was calculated by subtracting the endocardial volume from the epicardial volume, taking into account the myocardial specific gravity.

**STIR images:** Myocardial oedema was assessed by T2 weighted images, where the signal intensity (SI) in the myocardium is compared against the signal intensity in the skeletal muscle (myocardial SI/skeletal SI). A ratio above 1.9 indicates myocardial oedema (144).

**Native and postcontrast T1 maps & LGE images:** Myocardial fibrosis was quantified by T1 mapping techniques and LGE imaging. In T1 maps, a signal above  $1100\text{ms} \pm 50$  is regarded as elevated and therefore indicates presence of myocardial fibrosis, in the absence of abnormalities on T2 mapping and STIR imaging. T1 maps have also been shown to detect diffuse myocardial fibrosis often missed by LGE (48). LGE imaging was performed 10 to 20 minutes after intravenous (IV) injection of gadolinium (0.15 mmol/kg body weight). This type of imaging allows the observer to detect focal fibrosis and pattern of enhancement.

**Strain imaging:** The degree of deformation in a myocardial segment can be measured by strain analysis. The feature tracking method was applied to analyse myocardial strain. Endocardial and epicardial borders as well as the mitral valve annular plane were defined manually at end-diastole. Global longitudinal strain and strain rates was estimated from two long-axis steady state free precession (SSFP) cine images while circumferential and radial strains and strain rates were derived from the short-axis cine images.

**2D-phase contrast velocity-encoded (flow) imaging:** Phase contrast mapping was used to measure blood flow. Pulmonary and aortic valves were contoured to determine forward and backward blood, and to compare flow across the aorta to the main pulmonary artery.

### Clinical assessment

The evaluation of patients referred for RH included variables such as medical history (duration of hypertension, co-morbidities, number and class of antihypertensive medication), demographics (age, gender, race) and clinical data (clinic BP, heart rate, weight, height and body mass index [BMI]) as well as kidney function (eGFR volumes, CKD stage, renin and aldosterone levels). These assessed variables were obtained from the patients' clinical folders before patients were enrolled in the study.

### Echocardiography

Patients underwent an echocardiogram (Philips IE 33, Probe S5) which involved placing a transducer over the chest to capture sound waves from the heart. These sound waves echo back to the probe and are modified into pictures that can be seen on a video monitor. The echocardiographic report included study of the LV structure and function (RVID, IVS, LVID, LVPW, fraction shortening, ejection fraction, LV mass cubed), aortic valve (aorta, left atrium, peak gradient, mean gradient, peak velocity, left ventricular outflow tract diameter, aortic valve area), mitral valve (peak E velocity, peak A velocity, E.A ratio, MV DCT, E/E ratio), tricuspid valve (TAPSE) and pulmonary valve (peak velocity, peak gradient), diastolic dysfunction and with anatomic and functional study to complement CMR.

### Electrocardiography

All patients underwent 12-lead electrocardiography on the GE ECG machine (GE Medical Systems Information Technologies, Inc. 8200W, Tower Avenue, Milwaukee, WI, USA). The modified Cornell voltage criteria were used for the assessment of LVH and the following parameters were measured: QRS (ms), QT/QTcBaz (ms), PR (ms), P (ms), RR/PP (ms) and P/QRS/T (degrees).

### Applanation Tonometry

All patients underwent applanation tonometry on the Hypertension Diagnostics Inc machine, (Eagan, Minnesota, USA) for measurement of arterial elasticity, which is a non-invasive measure of BP and arterial waveform at the wrist. The following parameters were measured: average heart rate (bpm), average systolic BP (mmHg), average diastolic BP (mmHg), mean arterial BP (mmHg), pulse pressure (mmHg), large artery elasticity (ml/mmHg $\times$ 100), small artery elasticity (ml/mmHg $\times$ 100), systemic vascular resistance (dyne $\times$ sec $\times$ cm<sup>-5</sup>) and total impedance (dyne $\times$ sec $\times$ cm<sup>-5</sup>).

### Bloods

All biochemical assays were sent to the National Health and Laboratory Services, which is an internationally accredited laboratory. Details of the methodology of these tests can be found in their laboratory manual (<https://www.nhls.ac.za/diagnostic-services/type-of-tests/>). These biochemical assays taken in the Hypertension Clinic were used for comparison with imaging parameters to assess their role in determining the phenotype of hypertensive heart disease. Serum biomarkers of interest included renin, aldosterone and creatinine.

## Site

This study used UCT CUBIC , Department of Medicine, University of Cape Town and Groote Schuur Hospital as its main sites for primary investigation.

## Data collection, safety, monitoring and analysis Safekeeping

Data was collected by the researcher, Ms Pheletso Letuka, and recorded in an electronic database. As this is a low risk study, the collected data poses no threat to the participants' standard care. The patient's personal details and identity will not be used in subsequent publications. All information complied with the Data Protection Act, 1998. To maintain patient confidentiality, all data recorded and analysed was stored on a secure computer with strict access control gained only by the relevant researchers. Access to patient records was monitored by the study supervisors.

## Data Analysis

Binary data was presented as value (percentage) and continuous values were expressed as mean  $\pm$  standard deviation. Categorical data were analysed using the Chi-square test. Baseline variables for patients with RUH and RCH were analysed using the two-sample t-test where appropriate. Statistical significance level was set at 0.05. All analysis was performed using IBM SPSS, version 25 (IBM, Somers, New York, USA).

## Ethical considerations

This study was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC 494/2017). Patients from the Hypertension Clinic meeting the inclusion criteria were told about our study and what it aimed to do. Interested patients were provided with a patient information leaflet that explained the process of the study in greater detail, and a written consent form that they had to fill and sign. The original consent form was kept in each participant's file, while they kept their own copy. (Supporting documents can be found from page 91, Appendix 2-5.)

## Chapter 4: Results

### Baseline Characteristics

Of the 50 participants recruited in the study, 56% (n=28) were females and 44% (n=22) were males. 22% (n=11) were Black, 6% (n=3) were White, 4% (n=2) were Indian and 68% (n=34) were Mixed ancestry. From the study population, 30 patients were diagnosed with RUH, of these, 53% were female and 47% were male. (Tables 1.3 & 1.4). 20 patients were diagnosed with RCH, of these 60% were female and 40% were male. The mean age of the total study population was 40±12.9, however the RCH patients were younger (37±12.8) compared to the RUH group (43±14.7). The age difference between all groups was not statistically significant (p=0.17) (Table 1.4).

**Table 1.3: Demographic data (N= 50)**

Mean Age (years)	40±12.9
Male	22 (44%)
Female	28 (56%)
Black	11 (22%)
White	3 (6%)
Coloured	34 (68%)
Indian	2 (4%)
BMI (kg/m <sup>2</sup> )	33±8.2
Resistant Uncontrolled	30 (60%)
Resistant Controlled	20 (40%)

All continuous data are presented as mean ± SD unless otherwise indicated.

**Table 1.4: Demographic data separated by type of RH**

	<b>RUH N=30</b>	<b>RCH N=20</b>	<b>P Value</b>
Median Age (years)	42.6±12.9	37±12.8	0.17
Male	14 (47%)	8 (40%)	0.64
Female	16 (53%)	12 (60%)	
Height (m)	1.66	1.65	0.69
BSA (m <sup>2</sup> )	2	2.06	0.59
BMI (kg/m <sup>2</sup> )	32±7.8	34±8.1	0.37

All continuous data are presented as mean ± SD unless otherwise indicated.

#### Associated co-morbidities, clinical features and medical history

We assessed the different comorbidities associated with RUH, clinical features and medical history from patient files (Table 1.5&1.6). These included obesity, LVH, retinopathy, treatment regimen and duration of hypertension.

There were no significant differences between the RUH and the RCH group (p=0.8). In fact, both groups had similar obesity rates (73% vs. 70%). LVH was more common in the RUH (39%) versus the RCH group (20%) (Table 1.5).

Retinopathy was more common in patients with RUH, p=0.08 (Table 1.6). Patients with RUH were more likely to have a longer duration of hypertension, present with LVH and retinopathy, and were likely to be on medical therapy that included an ACE inhibitor or an angiotensin receptor , p=0.01 or doxazosin, p= 0.09 (Table 1.6).

**Table 1.5: Co-morbidities associated with RH and cardiovascular risk factors**

	<b>RUH N=30</b>	<b>RCH N=20</b>	<b>P Value</b>
Overweight, n (%)	2 (7%)	5 (25%)	0.07
Obesity, n (%)	22 (73%)	14 (70%)	0.80
Black race, n (%)	6 (20%)	5 (25%)	0.61
Smoking, n (%)	11 (39%)	5 (28%)	0.32

All continuous data are presented as mean  $\pm$  SD unless otherwise indicated.

**Table 1.6: Clinical features and medical history**

	<b>RUH N=30</b>	<b>RCH N=20</b>	<b>P Value</b>
Duration of hypertension(years)	10.5 $\pm$ 10.7	3.6 $\pm$ 3.4	0.02
Retinopathy	14 (61%)	4 (31%)	0.08
Albuminuria	10 (35%)	2 (14%)	0.15
Known history of LVH	9 (30%)	4 (20%)	0.69
Prior MI	3 (17%)	0	0.28
Heart Failure	1 (8%)	1 (17%)	0.54
ACE/ARB	26 (90%)	11 (58%)	0.01
CCB	22 (76%)	17 (90%)	0.21
Beta-Blocker	9 (31%)	3 (18%)	0.26
MRA	9(28%)	2 (11%)	0.14
Doxazosin	9 (31%)	2 (11%)	0.09
Diuretic therapy	29 (97%)	17 (90%)	0.31

All continuous data are presented as mean  $\pm$  SD unless otherwise indicated.

### Serum biomarkers

Blood samples collected in the Hypertension Clinic were sent for processing at the National Health Laboratory Services and the following serum biomarkers were analysed: renin, aldosterone, creatinine and eGFR according to MDRD formula. There were no significant differences in the analysed biomarkers between both patient groups (Table 1.7).

**Table 1.7: Laboratory results and serum biomarkers**

	<b>RUH N=30</b>	<b>RCH N=20</b>	<b>P Value</b>
Renin (miu/L)	151±223	86±120	0.37
Aldosterone (pmol/L)	378.7±256.8	407.5±249	0.74
Creatinine (umol/L)	96.8±103	109.2±139.7	0.72
eGFR (mL/min/1.73 m <sup>2</sup> )	57.3±9.7	57±12.1	0.9

All continuous data are presented as mean ± SD unless otherwise indicated.

### Applanation tonometry

Applanation tonometry was performed on all participants enrolled in the study. Results are shown in Table 1.8. Significant differences were noted between the 2 groups in systolic, diastolic and mean arterial BP, small artery elasticity and systemic vascular resistance. Patients with RUH had significantly higher systolic ( $p= 0.005$ ), diastolic ( $p= 0.02$ ) BP, mean arterial BP ( $p= 0.007$ ) and a trend for increased pulse pressure ( $p= 0.09$ ) and lower large artery elasticity ( $p=0.08$ ). Furthermore, they had significantly lower small artery elasticity compared to patients with RCH ( $p= 0.002$ ) and a higher systemic vascular resistance ( $p= 0.003$ ) compared to the RCH group.

**Table 1.8: Applanation tonometry findings**

	<b>RUH N=30</b>	<b>RCH N=20</b>	<b>P Value</b>
Average HR (bpm)	72.1±16.6	67.6±9.3	0.32
Average systolic BP (mmHg)	155.6±21.6	137.8±16.5	0.005
Average diastolic BP (mmHg)	88.4±14.5	77.5±13.6	0.02
Mean arterial BP (mmHg)	115.4±17.2	101±15.3	0.007
Pulse pressure (mmHg)	67.3±14.2	60.1±12.4	0.095
Large arterial elasticity (ml/mmHgx100)	12.5±4	14.7±3.8	0.08
Small arterial elasticity (ml/mmHgx100)	4.1±2.1	6.9±3.6	0.002
Systemic vascular resistance (dyneXsecXcm-5)	1754±418.4	1363±371.5	0.003
Total Impedence (dyneXsecXcm-5)	164.3±57.9	139.1±42.4	0.13

All continuous data are presented as mean ± SD unless otherwise indicated.

### Cardiovascular magnetic resonance

On CMR, the only significant difference noted between the two groups is the right ventricular end-systolic volume (RVESV). The RUH group had significantly lower RVESV compared to the RCH group (p=0.04). Conversely, the RUH group had a higher indexed left ventricular mass (LVMI) (p=0.06) and lower right ventricular end-diastolic volume (RVEDV) (p=0.09), none of which were significantly different. (Table 1.9). There were no differences in native T1, ECV and quantitative LGE values. Surprisingly, there were also no differences in strain and strain rates between the RUH and RCH groups.

**Table 1.9: CMR findings**

	<b>RUH N=30</b>	<b>RCH N=20</b>	<b>P Value</b>
LVEDV (ml)	152.6±28	150.3±33	0.79
LVESV (ml)	50.3±19.5	49.7±18.6	0.91
LVSV (ml)	105±26	100.5±20.6	0.5
LVEF (%)	67.4±9.1	67.4±7.2	0.99
LV Mass (g)	122.2±37.3	107.2±34.7	0.16
LVMI (g/m <sup>2</sup> )	61.6±17.6	52.9±13.9	0.06
LA Area (cm <sup>2</sup> )	20.2±5.1	18.6±4.1	0.25
LA Volume (ml)	65.9±24.4	62.7±19.5	0.63
LA Dimension (cm)	35.5±9.5	37.2±6.4	0.51
RVEDV (ml)	133.4±36.6	152.3±41	0.09
RVESV (ml)	60.5±20.8	75±28.4	0.04
RVSV (ml)	72.6±24.2	76.4±19.6	0.57
RVEF (%)	54.7±10.9	52.4±9.2	0.43
RA Volume (ml)	63.1±26.2	68.3±31.3	0.53
Native T1 Molli (ms)	1243±44	1236±57	0.64
Native T1 Shmolli (ms)	1155±57	1145±59.7	0.60
Postcontrast T1 Molli (ms)	651±47	677±94	0.2
Postcontrast T1 Shmolli (ms)	607±60	613±64	0.77
ECV(%)	0.28±0.04	0.29±0.03	0.71
Global Peak Radial Strain (%)	33.7±12.3	30.7±9.2	0.36
Global Peak Circ Strain (%)	-21.3±3.5	-20.7±2.7	0.51
Global Peak Long Strain (%)	-22.1±3.6	-20.6±2.8	0.11
Systolic Radial SR	2.3±1.1	2.0±0.5	0.2
Systolic Circ SR	-1.26±0.3	-1.23±0.17	0.72
Systolic Long SR	-1.27±0.3	-1.17±0.2	0.18
Diastolic Radial SR	-2.58±1.17	-2.38±0.9	0.51
Diastolic Circ SR	1.29±0.35	1.36±0.34	0.47
Diastolic Long SR	1.34±0.37	1.49±1.0	0.47

All continuous data are presented as mean  $\pm$  SD unless otherwise indicated.

### Echocardiographic and electrocardiographic findings

Patients with RUH were twice as likely to present with LVH on echo (Table 2.1). On ECG, no significant differences were noted between the RUH group and the RCH group (Table 2.2). Even though LVH on ECG was twice more in the RUH group, this did not meet statistical significance.

Table 2.1: Echocardiographic data

	<b>RUH N=30</b>	<b>RCH N=20</b>	<b>P Value</b>
RVIDd(cm)	1.74 $\pm$ 0.45	2.0 $\pm$ 0.57	0.17
RVIDs (cm)	1.0	1.45 $\pm$ 0.64	0.67
IVSd (cm)	1.32 $\pm$ 0.2	1.19 $\pm$ 0.16	0.08
IVSs (cm)	1.7 $\pm$ 0.29	1.58 $\pm$ 0.21	0.26
LVIDd (cm)	4.75 $\pm$ 0.34	4.94 $\pm$ 0.49	0.21
LVIDs (cm)	2.9 $\pm$ 0.48	3.0 $\pm$ 0.39	0.51
LVPWd (cm)	1.18 $\pm$ 0.19	1.07 $\pm$ 0.15	0.13
LVPWs (cm)	1.56 $\pm$ 0.29	1.6 $\pm$ 0.17	0.68
FS (%)	36.8 $\pm$ 5.4	38 $\pm$ 3.9	0.53
LVEF (%)	66.2 $\pm$ 6.85	68.3 $\pm$ 4.6	0.37
E/A ratio	1.25 $\pm$ 0.59	1.27 $\pm$ 0.46	0.92
MV DCT	201 $\pm$ 43.7	192.2 $\pm$ 15.8	0.53
LVMl (g/m <sup>2</sup> )	214 $\pm$ 59	204 $\pm$ 66	0.66
Dilated LV, n (%)	0	1 (8%)	0.21
LVH, n (%)	16 (84%)	5 (42%)	0.01

All continuous data are presented as mean  $\pm$  SD unless otherwise indicated.

**Table 2.2: ECG findings**

	<b>RUH N=30</b>	<b>RCH N=20</b>	<b>P Value</b>
Heart Rate (bpm)	71.4±16.9	68.1±9.4	0.44
Normal Rhythm	22 (73%)	13 (68%)	
Bradycardia	2 (%)	0	0.32
Tachycardia	1 (%)	3 (%)	
Arrhythmias	1 (3%)	3 (16%)	
Atrial Fibrillation	5	3	
Other	0	0	
QRS Duration (ms)	96±11.9	95.5±15.9	0.89
QTc (ms)	434.4±26.8	416.2±93	0.32
PR (ms)	156.7±24.4	163.7±27.5	0.36
Repolarization abnormalities (%)	2(7%)	0	0.46
LVH (%)	11 (37%)	3 (16%)	0.11

All continuous data are presented as mean ± SD unless otherwise indicated.

## Chapter 5: Discussion

This study used a multimodal approach to define the phenotype and imaging characteristics of patients with RUH and RCH. According to the best of our knowledge, this is the first study to define the phenotype of such patients with using a multiparametric approach, including CMR. Further, this is the first such study from SSA.

We included 30 patients with RUH and 20 patients with RCH. Patients with RUH were older, with a longer duration of hypertension, and more likely to be on therapy that included an ACE inhibitor or ARB. RUH patients also have more LVH, increased LVMI and reduced RVESV. Further, RUH patients had greater vascular abnormalities including higher systolic BP, higher diastolic BP, higher mean arterial pressure and higher systemic vascular resistance. In keeping with these results, RUH patients had lower large and small artery elasticity. On CMR, no differences were noted in global strain, diastolic and systolic strain rates between the two groups. There were also no differences noted in native T1, ECV (measures of diffuse myocardial fibrosis) and LGE volume fraction (a measure of focal myocardial fibrosis) between RUH and RCH, with all these measures increased in both groups. In summary, our observations confirm our hypothesis that RUH represents a unique phenotype of hypertension with greater cardiovascular involvement and a more severe phenotype, which may explain the excess CV morbidity and mortality associated with RUH.

### *LV adaptations: concentric LVH or concentric remodeling*

Concentric LVH is defined by an increase in LV mass, increased global LV wall thickening in response to pressure overload and a normal LV cavity size. Concentric LVH tends to be prevalent in middle-aged and elderly patients, and is closely linked to increased cardiac output (49,145). In our study, on echo, both patient groups had elevated LVMI however there were no significant differences between the two groups. We were unable to separate the LV phenotype with regards to LVMI. On CMR, patients with RUH had increased LVMI compared to patients with RCH, however, LVMI for both groups still fell within normal ranges indexed for males and females. We found normal LV cavity sizes for both groups, with an average of 4.9cm in LVEDD (normal <5.6cm).

Structural adaptations in the LV are not only limited to the presence of hypertrophy, but also include geometric changes (146). Concentric remodeling is a result of long-standing hypertension and is usually marked by normal LV mass, normal LV cavity size and increased LV wall thickness. These patterns suggest concentric remodeling as opposed to overt concentric hypertrophy. Cuspidi *et al*, reported that concentric hypertrophy is not the most commonly observed geometric pattern in hypertension; in their study, it was as seldomly seen as eccentric hypertrophy (147-149). However, patients with concentric remodeling have a similar prognosis to those with concentric hypertrophy (150). Based on our results, we surmise that concentric LV remodeling was more common in patients with RUH, whereas patients with RCH presented with a normal LV phenotype.

### *LV diastolic dysfunction*

Diastolic function can be assessed noninvasively using the preferred technique of echocardiography or CMR. Myocardial strain measures the degree of change from resting

length to maximum length. Strain rate measures the rate at which these deformations occur (151). In our study, there was no evidence of left ventricular diastolic dysfunction in both groups (on echocardiography as shown by the E/A ratios in Table 2.1, both of which are considered normal. These observations were replicated on CMR, as both groups of patients had normal strain results without any significant intergroup differences. Our results are similar to a study of LV phenotypes in HHD which found similar strain and strain rates without any intracellular or extracellular myocardial changes in different forms of HHD (152). In previous studies, diastolic dysfunction has been reported in patients with hypertension in SSA, this differs from our results because we did not report diastolic dysfunction on CMR and echo. This might be due to differences in imaging modality (echo vs CMR) or differences in LV geometry (eccentric hypertrophy vs concentric hypertrophy vs concentric remodeling.) Interestingly, in this study, such as ours, aortic stiffness was severely increased in patients with concentric remodeling compared to patients with concentric and eccentric LVH.

#### *LV systolic function and LV geometry*

We used CMR to assess ventricular function by measuring LV volumes and function. RUH and RCH patients had similar LVEDV, LVESV, LVSV and LVEF. These observations were like many other studies of hypertension where LV volumes and function remained normal. It has been postulated that chamber dilatation in HHD occurs in response to volume overload (153). Impairment in LV systolic function appears to be positively correlated to LV chamber dilatation in patients with eccentric remodeling (154). Demographic factors such as race and ethnicity can also modulate the manner in which the LV responds to an elevation in

BP. For instance, blacks compared with whites appear to be predisposed to a concentric hypertrophic response (155-157), although it is uncertain whether this represents an effect independent of BP (158). In isolated systolic hypertension, women are more likely to develop concentric LVH, and men were more likely to develop eccentric LVH (159). Advancing age has also been associated with a concentric as opposed to eccentric hypertrophic response in hypertension on echocardiography and CMR (160,161).

Other medical conditions common in HHD, such as diabetes, obesity, and CAD, can also affect the pattern of hypertrophic response. CAD has been shown to be associated with an increased LV diastolic dimension and a higher prevalence of eccentric LVH (162). Diabetes mellitus has been associated with a concentric hypertrophic response, as measured by increased relative wall thickness (160,163), whereas obesity, characterised as a volume-overload state, has been associated predominantly with eccentric hypertrophy (164,165).

#### *RV function*

The involvement of the RV in systemic hypertension is understudied. Furthermore, there is a lack of such data using CMR. We used CMR to study RV volumes and function and noted that patients with RUH had reduced RVESV. Galea *et al* (166) reported that RV involvement in other cardiac conditions has CMR features that often resemble LV patterns, likely reflecting ventricular interdependence. Because the heart functions as a single unit, structural and functional changes that occur in the LV, also ultimately affect the RV (78). Ventricular interdependence involves forces that are transmitted from one ventricle to the adjacent one, through the myocardium and interventricular septum. This mechanism occurs independently from hormonal, circulatory or neural control. About 20%-40% of the per beat RV systolic function and volume is dependent on LV contraction (79). Ventricular

interdependence occurs mainly due to the ventricles' close anatomic association: sharing common muscle fibres and a septal wall.

In a study by Todiere and colleagues, 25 patients with uncomplicated, mild to moderate essential hypertension were compared to 24 healthy, age- and gender-matched controls using CMR, RV mass index (RVMI), ventricular wall thickness and remodeling index were greater in hypertensive participants and associated with reduced peak filling rate (80). The same group also demonstrated that systemic hypertension leads to RV remodeling and impaired diastolic function (80,81), explaining, in part, why the pulmonary circulation and the RV are not immune to the effects of systemic hypertension.

### *Myocardial fibrosis*

Myocardial fibrosis is the common final pathway of many cardiac pathologies and can either appear as focal (due to cell death via apoptosis, autophagy or necrosis), or it can be diffuse (following accelerated collagen deposition within the extracellular space, as in hypertension) (167). Our study used different CMR techniques to detect myocardial fibrosis in RUH and RCH patients. ECV is a powerful indicator of myocardial tissue remodeling and is advantageous as it allows detection of early fibrotic-related changes, otherwise missed by conventional LGE (48). Increased ECV is mostly indicative of excessive collagen deposition within the extracellular space of the myocardium, thus making ECV a robust measurement of myocardial fibrosis (167).

Our native T1, post-contrast and ECV values were all normal. We also did not find any differences between the RUH and RCH patients. Normal pre and post-contrast T1 maps and normal ECV values successfully highlight the lack of myocardial fibrosis in patients with

resistant uncontrolled and resistant controlled hypertension (152), highlighting yet again, the concentric remodeling phenotype in the resistant uncontrolled group, and the normal LV phenotype in the resistant controlled group. This finding could perhaps explain, in part, why both groups of patients lack myocardial disarray as is often seen in hypertensive heart disease.

### *Vascular adaptations*

On applanation tonometry, patients with RUH had significantly higher systolic and diastolic BP and mean arterial BP. They also showed lower vascular elasticity in the large and small vessels and had higher systemic vascular resistance. Reduced arterial elasticity has been linked to hypertension (168). Patients with RUH had significantly increased systemic vascular resistance compared to RCH, consistent with other publications (169).

BP is a product of cardiac output (heart rate x stroke volume) x systemic vascular resistance (SVR) (170). Often hypertensive patients tend to have increased cardiac output, increased systemic vascular resistance or both (170). In fact, increased arterial stiffness and increased systemic vascular resistance seem to play a crucial role in the vicious cycle between endothelial dysfunction and perpetuated high BP (170).

Most studies have also shown the CV consequences associated with reduced arterial elasticity. Hypertension leads to oxidative stress (171,172), which in turn, leads to decreased expression of endogenous nitric oxide synthase (eNOS) and decreased eNOS uncoupling (172). Both states ultimately lead to suppressed nitric oxide (NO) activity, which is implicated in endothelial dysfunction (173,174). Arterial stiffness is a marker of endothelial

dysfunction, which includes regulatory changes leading to abnormal vasomotion and the expression of a prothrombotic and proinflammatory phenotype of the vascular endothelium (175). Impaired elasticity encompasses alterations in vascular biology and function, particularly vasomotor function, and is a predictor of adverse CV outcomes (176). Alterations in the small artery lead to vascular abnormalities affecting the kidneys and resulting in microalbuminuria, retinopathy and cerebral microcirculatory disease (176). Structural alterations in conduit arteries lead to large artery dysfunction, which has been shown to increase the risk of CV morbidity and mortality (176). This is consistent with our findings. As shown in the applanation tonometry results, patients with resistant uncontrolled hypertension have reduced vascular elasticity and increased systemic resistance. These are the group of patients who are more likely to present with adverse CV outcomes in the future.

### *Pharmacological therapy*

Patients with RUH were more likely to be on an ACE inhibitor or ARB and an alpha blocker. The benefits of combination therapy have been demonstrated in multiple studies, particularly by combining an ACE inhibitor or ARB, a long acting CCB and a thiazide diuretic. The aim is to use therapeutic agents with different pharmacological actions to lower BP (177). In our study, RUH patients had higher systemic vascular resistance, and stood to benefit from multidrug combinations of antihypertensives. ACE inhibitors function by blocking the formation of angiotensin II (a vasoconstrictor) by inhibiting ACE (an enzyme that converts angiotensin I into angiotensin II). ACE inhibitors have also been shown, besides their vasodilative properties, to promote natriuresis and diuresis (178). ARBs function differently: blocking angiotensin II from binding to the angiotensin II Type 1 (AT1) receptor, therefore triggering vasodilation and natriuresis (178). Alpha blockers function by blocking

the sympathetic activity on blood vessels, by binding to the alpha-adrenoceptors in the vascular smooth muscle. They compete with norepinephrine (a neurotransmitter that promotes contraction on vascular smooth muscles (179). Ceral *et al* investigated the efficacy of doxazosin in patients with RH and found high tolerance and efficacy of alpha blockade in drug-resistant hypertension (180).

### *Conclusion*

HHD exhibits a host of different structural adaptations within various hypertensive phenotypes, which are well documented on CMR and echocardiography, as well as other supportive diagnostic tools such as ECG and applanation tonometry. RUH is an extreme phenotype that is largely characterised by concentric remodeling, increased LVMI compared to patients with resistant controlled hypertension, reduced arterial elasticity and increased systemic vascular resistance as well as altered RV function. We surmise that RUH patients may have a poorer prognosis due to their concentric remodeling phenotype, which is a risk factor for cardiovascular mortality and morbidity.

## Chapter 6: Limitations and future recommendations

This study had several limitations. First, the sample size of patients with RUH and RCH was relatively small. Secondly, the major limitation of this data was the lack of age-, sex- and ethnicity-matched controls as shown in tables 1.3 and 1.4. While we have control data for the different measures used in this study from several prior studies, these controls could not be used as their data was not available for all the measures and was not acquired contemporaneously, as in this study. Nonetheless, despite these limitations, this study still provides important insights into cardiovascular remodeling and phenotypes of cardiovascular disease in hypertension.

Several unanswered questions remain:

1. The long-term outcomes of the 2 phenotypes studies are not known in our population.
2. The imaging biomarkers that determine outcomes warrant further investigation.
3. The heart-brain axis in patients with RUH has not been adequately studied.
4. The role of the microbiome in mediating phenotypes of hypertension, treatment response and clinical outcomes has not been studied.

These and other questions will form the basis of the doctoral work for the masters student in this project, and will be conducted in a larger prospective study.

## References

1. Mayosi BM., The burden of non-communicable diseases in South Africa. *The Lancet*, 2009;374. 934-947.
2. Abegunde DO.,The burden and costs of chronic diseases in low-income and middle income countries. *The Lancet* 2007;370. 1929-1938.
3. World Health Organization, 2014. Global status report on non communicable diseases 2014: “attaining the nine global noncommunicable diseases targets; a shared responsibility”. Geneva: World Health Organization.
4. Lorell BH, Left Ventricular Hypertrophy: Pathogenesis, Detection, and Prognosis. *Circulation*, 2000;102. 470-479.
5. Richie J, Nansseu N., The highly neglected burden of resistant hypertension in Africa: a systematic review and meta-analysis. *BMJ Open*, 2016;6.
6. Forouzanfar MH., GBD 2013 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis. *The Lancet*, 2015;386. 2287-1323.
7. Ataklte F., Burden of undiagnosed hypertension in sub-Saharan Africa: a systematic review and meta-analysis. *Hypertension*, 2015;65. 291-298.
8. Addo J et al., Hypertension In Sub-Saharan Africa. *Hypertension*, 2007;50. 1012-1018.
9. Addo J., Hypertension in sub-Saharan Africa: a systematic review.*Hypertension*, 2007;50. 1012-1018.

10. Seedat YK., Recommendations for hypertension in sub-Saharan Africa. ***Cardiovascular Journal of South Africa***, 2004;15. 157-158.
11. Zuhlke, L., 2016. The Conversation Africa. [Online] Available at: <https://theconversation.com/why-heart-disease-is-on-the-rise-in-south-africa-66167> [Accessed 12 April 2017].
12. Seedat, Y., Why is control of hypertension in sub-Saharan Africa poor?. ***Cardiovascular Journal of Africa***, 2015;26(4). 1.
13. Ntusi, N. A., Dismal management of hypertension at primary level. ***Cardiovascular Journal of Africa***, 2011; 22(4). 172.
14. Kearney, P., Global Burden of Hypertension. ***The Lancet***, 2005; 364(9455). 217-223.
15. Ezzati, M., Selected Major Risk Factors and Global and Regional Burden of Disease. ***The Lancet***, 2002; 360(9343). 1347-1360.
16. Rayner, B., Hypertension: Detection and Management in South Africa. ***Nephron Clinical Practice***, 2010; 116. 269-273.
17. Stewart, S., The Clinical Consequences and Challenges of Hypertension in Urban-dwelling Black Africans: Insights from the Heart of Soweto Study. ***International Journal of Cardiology***, 2011; 146(1). 22-27.
18. Zbigniew G et al., Blood Pressure Control and Primary Prevention of Stroke: Summary of the Recent Clinical Trial Data and Meta-Analyses. ***Current Hypertension Reports***, 15(6). 559-574.
19. Calhoun D.A et al., Resistant Hypertension: Diagnosis, Evaluation, and Treatment: A Scientific Statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. ***Circulation***, 2008; 117. 510-526.

20. Doménech M et al., Misdiagnosis of resistant hypertension: Real frequency of true resistant hypertension in patients with suspected resistance to treatment. *Med Clin (Barc)*, 2018; 150(1). 20-23.
21. Acelajado M.C et al., Refractory Hypertension: Definition, Prevalence and Patient Characteristics. *Journal of Clinical Hypertension*, 2012; 14. 7-12.
22. Carey, R. M., Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement from the American Heart Association. *Hypertension*, 2018; 72. e53-e90.
23. Dudenbostel T et al., Refractory versus resistant hypertension: Novel distinctive phenotypes. *Journal of Natural Sciences*, 2017; 3(9). 1-15.
24. Khosla, N., Are Chlorthalidone and Hydrochlorothiazide Equivalent Blood-Pressure-Lowering Medications?. *Journal of Clinical Hypertension*, 2005; 7(6). 354-356.
25. Gaddam K et al., Rapid reversal of left ventricular hypertrophy and intracardiac volume overload in patients with resistant hypertension and hyperaldosteronism: a prospective clinical study. *Hypertension*, 2010; 55(5). 1137-1142.
26. Jones E, Owen P, Rayner B et al., The R563Q mutation of the epithelial sodium channel beta-subunit is associated with hypertension. *Cardiovascular Journal of Africa*, 2012; 22(5). 241-244.
27. Rayner B, Jones E., The prevalence and relationship to hypertension of the R563Q mutation of the epithelial sodium channel in Southern Africa. *Cardiovascular Journal of Africa*, 2011; 22. S21.

28. Spence, D., Lessons From Africa: The Importance of Measuring Plasma Renin and Aldosterone in Resistant Hypertension. *Canadian Journal of Cardiology*, 2012; 28. 254–257.
29. Jones E, Rayner B, Owen P., The Association of the R563Q Genotype of the ENaC With Phenotypic Variation in Southern Africa. *American Journal of Hypertension*, 2012; 25(12). 1286-1291.
30. Hattangady N et al., Acute and Chronic Regulation of Aldosterone Production. *Molecular and Cellular Endocrinology*, 2012; 350(2). 151–162.
31. Schiffrin, M. B., Vascular Actions of Aldosterone. *Journal of Vascular Research*, 2012; 50. 89–99.
32. Itoh H., Mineralocorticoid Receptor-Associated Hypertension and Its Organ Damage: Clinical Relevance for Resistant Hypertension. *American Journal of Hypertension*, 2012; 5(5). 514–523.
33. Xanthakis V, Vasan R., Aldosterone and the Risk of Hypertension. *Current Hypertension Reports*, 2013; 15(2). 102–107.
34. Tobe S, Lewanczuk R., Resistant hypertension. *Canadian Journal of Cardiology*, 2009; 25(5). 315-317.
35. Noubiap J et al., 2018. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. [Online] Available at: <https://heart.bmj.com/content/heartjnl/early/2018/08/07/heartjnl-2018-313599.full.pdf> [Accessed 13 October 2018].
36. Judd E., Apparent and true resistant hypertension: definition, prevalence and outcomes. *Journal of Human Hypertension*, 2014; 28. 434-468.

37. Achelrod D et al., Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. *American Journal of Hypertension*, 2015; 28. 355-361.
38. Lotufo PA, Pereira A, Vasconcelos P., Resistant hypertension: risk factors, subclinical atherosclerosis, and comorbidities among adults-the Brazilian Longitudinal Study of Adult Health. *Journal of Clinical Hypertension*, 2015; 17. 74-80.
39. Sim JJ, Bhandari SK, Shi J et al., Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. *Mayo Clinic Proceedings*, 2013; 88(10). 1099-1107.
40. Calhoun D., Refractory and Resistant Hypertension: Antihypertensive Treatment Failure versus Treatment Resistance. *Korean Circulation Journal*, 2016; 46(5). 593-600.
41. Calhoun D, Pimenta E, David A., Resistant Hypertension: Incidence, Prevalence and Prognosis. *Circulation*, 2012; 125(13). 1594–1596.
42. Daugherty S, Powers JD, Magid DJ et al., Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients. *Circulation*, 2012; 125(13). 1635–1642.
43. Sim JJ, Bhandari SK, Shi J et al., Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and non-resistant hypertension. *Kidney International*, 2015; 88(3). 622-632.
44. Acelajado MC., Refractory Hypertension: Definition, Prevalence and Patient Characteristics. *Journal of Clinical Hypertension*, 2012; 14, pp. 2-7.
45. Logan M, High Prevalence of Unrecognized Sleep Apnea in Drug-Resistant Hypertension. *Journal of Hypertension*, 2001; 19. 2271-2277.

46. Pierdomenico, L., Cardiovascular Outcome in Treated Hypertensive Patients with Responder, Masked, False resistant and True Resistant Hypertension. ***American Journal of Hypertension***, 2005; 18. 1422-1428.
47. Isaksson, Prognosis in Therapy-Resistant Hypertension. ***Journal of Internal Medicine***, 1994; 236. 643-649.
48. Maceira AM, Mohiaddin RH., Cardiovascular magnetic resonance in systemic hypertension. ***Journal of Cardiovascular Magnetic Resonance***, 2012; 14(28). 2.
49. Drazner MH., The Progression of Hypertensive Heart Disease. ***American Heart Association Journals***, 2011; 123. 327.
50. Teoa LY, Chana LL, Lam C., Heart failure with preserved ejection fraction in hypertension. ***Current Opinion in Cardiology***, 2016; 31(4) 410-416.
51. Devereux, R., Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. ***Circulation***, 1977; 55(4) 613-618.
52. Myerson S, Francis J, Neubauer S., Oxford Specialist Handbooks in Cardiology: ***Cardiovascular Magnetic Resonance***. 2010; 1st ed. Oxford: Oxford University Press.
53. Alfakih K, Walters K, Jones T et al., New Gender-Specific Partition Values for ECG Criteria of Left Ventricular Hypertrophy: Recalibration Against Cardiac MRI. ***Hypertension***, 2004; 44(2) 175-179.
54. Berk BC, Fujiwara K, Lehoux S., ECM remodeling in hypertensive heart disease. ***Journal of Clinical Investigation***, 2007; 117(3) 568-575.
55. Spinale FG., Myocardial Matrix Remodeling and the Matrix Metalloproteinases: Influence on Cardiac Form and Function. ***Physiological Reviews***, 2007; 87(4) 1285-1342.

56. Schwartzkopff B., Structural and functional alterations of the intramyocardial coronary artery. *Circulation*, 1993; 88. 993-1003.
57. Olson J., Cardiac Plasticity. *New England Journal Of Medicine*, 2008; 358. 1370-1380.
58. Levy D, Garrison R, Savage D et al., Prognostic Implications of Echocardiographically Determined Left Ventricular Mass in the Framingham Heart Study. *New England Journal of Medicine*, 1990; 322. 1561-1566.
59. Devereux RB, Wachtell K, Gerds E et al., Prognostic Significance of Left Ventricular Mass Change During Treatment of Hypertension. *JAMA*, 2004; 292(19) 2350-2356.
60. Ganau A, Devereux RB, Roman MJ et al., Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *Journal of the American College of Cardiology*, 1992; 19(7) 1550-1558.
61. Ross J., On Variations in the Cardiac Hypertrophic Response to Pressure Overload. *Circulation*, 1997; 95(6) 1349–1351.
62. Sarong M., Hypertrophic Cardiomyopathy Phenotype Revisited After 50 Years With Cardiovascular Magnetic Resonance. *Journal of the American College of Cardiology*, 2009; 54(2) 220-228.

63. Muiesan M, Salvetti M, Monteduro C et al., Left Ventricular Concentric Geometry During Treatment Adversely Affects Cardiovascular Prognosis in Hypertensive Patients. ***American Heart Journals: Hypertension***, 2004; 43(4) 731-738.
64. Pennell DJ, Sechtem UP, Higgins CB et al., Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. ***European Heart Journal***, 2004; 25(21) 1940-1965.
65. Olsen MH, Wachtell K, Hermann KL et al., Is cardiovascular remodeling in patients with essential hypertension related to more than high blood pressure? A LIFE substudy. ***American Heart Journal***, 2002; 144(3) 530-537.
66. Matthias FG., Telmisartan Effectiveness on Left ventricular MAss Reduction (TELMAR) as assessed by magnetic resonance imaging in patients with mild-to-moderate hypertension — a prospective, randomised, double-blind comparison of telmisartan with metoprolol over a perio. ***Journal of the Renin-Angiotensin-Aldosterone System***, 2003; 4(4) 234-243.
67. Pitt B, Reichek N, Willenbrok R et al., Effects of Eplerenone, Enalapril, and Eplerenone/Enalapril in Patients With Essential Hypertension and Left Ventricular Hypertrophy: The 4E–Left Ventricular Hypertrophy Study. ***American Heart Journal: Circulation***, 2003; 108(15) 1831-1838.

68. Reichek N, Devereux RB, Rocha RA et al., Magnetic Resonance Imaging Left Ventricular Mass Reduction With Fixed-Dose Angiotensin-Converting Enzyme Inhibitor–Based Regimens in Patients With High-Risk Hypertension. ***American Heart Journal: Hypertension***, 2009; 54(4) 731-738.
69. Solomon SD, Appelbaum E, Manning WJ et al., Effect of the Direct Renin Inhibitor Aliskiren, the Angiotensin Receptor Blocker Losartan, or Both on Left Ventricular Mass in Patients With Hypertension and Left Ventricular Hypertrophy. ***American Heart Journal: Circulation***, 2009; 119(4) 530-537.
70. Maceira AM, Joshi J, Prasad SK et al., Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. ***American Heart Journal: Circulation***, 2009; 111(2) 189-193.
71. Vogelsberg H, Mahrholdt H, Dekeugi CC et al., Cardiovascular Magnetic Resonance in Clinically Suspected Cardiac Amyloidosis: Noninvasive Imaging Compared to Endomyocardial Biopsy. ***Journal of the American College of Cardiology***, 2008; 51(10) 1022-1030.
72. Puntmann VO, Jahnke C, Gebker R et al., Usefulness of Magnetic Resonance Imaging to Distinguish Hypertensive and Hypertrophic Cardiomyopathy. ***American Journal of Cardiology***, 2010; 106(7), pp. 1016-1022.

73. Petersen., Differentiation of athlete's heart from pathological forms of cardiac hypertrophy by means of geometric indices derived from cardiovascular magnetic resonance. *Journal of Magnetic Vascular Resonance*, 2005; 7(3) 551-558.
74. Fiorentini C., Pulmonary vascular over-reactivity in systemic hypertension. A pathophysiological link between the greater and the lesser circulation. *Hypertension*, 1985; 7. 995-1002.
75. Lu KJ., Right ventricular global longitudinal strain is an independent predictor of right ventricular function: a multimodality study of cardiac magnetic resonance imaging, real time three-dimensional echocardiography and speckle tracking echocardiography. *Echocardiography*, 2015; 32. 966-974.
76. Schermuly RT, Ghofrani HA, Wilkins RM et al., Mechanisms of disease: pulmonary arterial hypertension. *Natural reviews Cardiology*, 2011; 8(8) 443-455.
77. Tadic M, Cuspidi C, Bombelli M et al., Right heart remodeling induced by arterial hypertension: Could strain assessment be helpful?. *The Journal of Clinical Hypertension*, 2018; 20(2) 400-407.
78. Akintunde AA, Akinwusi PO, Familoni OB et al., Effect of systemic hypertension on right ventricular morphology and function: an echocardiographic study. *Cardiovascular Journal of Africa*, 2010; 21(5) 252-256.

79. Santamore WP, Dell'Italia LJ., Ventricular interdependence: Significant left ventricular contributions to right ventricular systolic function. ***Progress in Cardiovascular Diseases***, 1998; 40(4) 289-308.
80. Karaye KM, Bonny A., Right ventricular dysfunction in systemic hypertension: A call to action. ***International Journal of Cardiology***, 2016; 206. 51-53.
81. Ilieva A, Kotova G, Dimitrov IN et al., Hypertension-induced changes in the rat myocardium during the development of cardiac hypertrophy – a comparison between the left and the right ventricle. ***Acta Histochemica***, 2019; 121 (1) 16-28.
82. Levick SP, Widiapradja A., Mast Cells: Key Contributors to Cardiac Fibrosis. ***International Journal of Molecular Sciences***, 2018; 19(1) 231.
83. Levick SP, Meléndez GC, Plante E et al., Cardiac mast cells: the centrepiece in adverse myocardial remodelling. ***Cardiovascular Research***, 2011; 89(1) 12-19.
84. Todiere G, Neglia D, Ghione S et al., Right ventricular remodelling in systemic hypertension: a cardiac MRI study. ***BMJ:Heart***, 2011; 97(15) 1257-1261.
85. Weber KT, Sun Y, Bhattacharya SK et al., Myofibroblast-mediated mechanisms of pathological remodelling of the heart. ***Nature Reviews Cardiology***, 2013; 10. 15-26.
86. Jellis C, Martin J, Narula J et al., Assessment of Nonischemic Myocardial Fibrosis. ***The American Journal of Cardiology***, 2010; 56(2) 89-97.

87. Gyöngyösi M, Winkler J, Ramos I et al., Myocardial fibrosis: biomedical research from bench to bed side. *European Journal of Heart Failure*, 2017; 19. 177-191.
88. Li A, Liu PP, Villarreal FJ et al., Dynamic Changes in Myocardial Matrix and Relevance to Disease. *American Heart Journal: Circulation Research*, 2014; 114(5) 916-927.
89. Kong P, Christia P, Frangogiannis NG., The pathogenesis of cardiac fibrosis. *Cellular and Molecular Life Sciences*, 2014; 71(4) 549-574.
90. Weber K., Patterns of myocardial fibrosis. *Journal of Molecular Cell Cardiology*, 1989; 5. 121-131.
91. Heymans S, González A, Pizard A et al., Searching for new mechanisms of myocardial fibrosis with diagnostic and/or therapeutic potential. *European Journal of Heart Failure*, 2015; 17(8) 764-771.
92. Camelliti P, Borg TK, Kohl P., Structural and functional characterisation of cardiac fibroblasts. *Journal of Cardiovascular Research*, 2005; 65(1) 40-51.
93. López B, Querejeta R, González A et al., Collagen Cross-Linking But Not Collagen Amount Associates With Elevated Filling Pressures in Hypertensive Patients With Stage C Heart Failure. *American Heart Association: Hypertension*, 2012; 60(3) 677-683.

94. Izawa H, Murohara T, Nagata K et al., Mineralocorticoid Receptor Antagonism Ameliorates Left Ventricular Diastolic Dysfunction and Myocardial Fibrosis in Mildly Symptomatic Patients With Idiopathic Dilated Cardiomyopathy. **American Heart Association: Circulation**, 2005; 112(19) 2940-2945.
95. McLenachan J., Ventricular arrhythmias in hypertensive left ventricular hypertrophy. Relationship to coronary artery disease, left ventricular dysfunction, and myocardial fibrosis. **American Journal of Hypertension**, 1990; 3(10) 735-740.
96. Kawara, T., Activation delay after premature stimulation in chronically diseased human myocardium relates to the architecture of interstitial fibrosis. **American Heart Association: Circulation**, 2001; 104(25) 3069-3075.
97. Anderson KP, Walker R, Urie P et al., Myocardial Electrical Propagation in Patients with Idiopathic Dilated Cardiomyopathy. **The Journal of Clinical Investigation**, 1993; 92(1) 122-140.
98. Schwartzkopff B, Brehm M, Mundhenke M et al., Repair of coronary arterioles after treatment with perindopril in hypertensive heart disease. **Hypertension**, 2000; 36(2) 220-225.
99. Segura AM., Fibrosis and heart failure. **Heart Failure Reviews**, 2014; 19(2) 173-185.

100. Díez, J, López B, González A & Querejeta R., Clinical aspects of hypertensive myocardial fibrosis. ***Current Opinion in Cardiology***, 2001; 16(6) 328-335.
101. Rudolph A, Adel-Aty H, Bohl S et al., Noninvasive Detection of Fibrosis Applying Contrast-Enhanced Cardiac Magnetic Resonance in Different Forms of Left Ventricular Hypertrophy: Relation to Remodeling. ***Journal of the American College of Cardiology***, 2009; 53(3) 284-291.
102. Mewton N, Liu CY, Croisille P et al., Assessment of Myocardial Fibrosis With Cardiovascular Magnetic Resonance. ***Journal of the American College of Cardiology***, 2011; 57(22) 891-903.
103. Mohiaddin RH, Maceira AM, Raad H., Cardiovascular magnetic resonance in systemic hypertension. ***Journal of Cardiovascular Magnetic Resonance***, 2012; 14(28) 4-8.
104. Maceira AM, Joshi J, Prasad SK et al., Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. ***American Heart Association: Circulation***, 2005; 111(2) 186-193.
105. Kim RJ, Wu E, Rafael A et al., The Use of Contrast-Enhanced Magnetic Resonance Imaging to Identify Reversible Myocardial Dysfunction. ***The New England Journal of Medicine***, 2000; 343. 1445-1453.

106. Moon JC, Sheppard MN, Ikington AG et al., The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. ***Journal of the American College of Cardiology***, 2004; 43(12) 2260-2264.
107. Krittayaphong R, Boonyasirinant T, Chaithiraphan V et al., Prognostic value of late gadolinium enhancement in hypertensive patients with known or suspected coronary artery disease. ***The International Journal of Cardiovascular Imaging***, 2010; 26(1) 123-131.
108. Messroghli DR, Walters K, Plein S et al., Myocardial T1 mapping: Application to patients with acute and chronic myocardial infarction. ***Magnetic Resonance in Medicine***, 2007; 58(1) 34-40.
109. Ugander M, Oki A, Hsu LY et al., 2012. Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology. ***European Heart Journal***, 2012; 23(10) 1268-1278.
110. Lee JJ, Liu S, Nacif MS et al., Myocardial T1 and extracellular volume fraction mapping at 3 Tesla. ***Journal of Cardiovascular Magnetic Resonance Imaging***, 2011; 13(75) 1-10.
111. Piechnik SK, Ferreira VM, Dall'Armellina E et al., Shortened Modified Look-Locker Inversion recovery (ShMOLLI) for clinical myocardial T1-mapping at 1.5 and 3 T within

- a 9 heart-beat breath-hold. *Journal of Cardiovascular Magnetic Resonance*, 2010; 12(69) 1-11.
112. White SK, Piechnik SK, Neubauer S et al., Histological validation of ShMOLLI equilibrium contrast CMR for the measurement of diffuse myocardial fibrosis. *Journal of Cardiovascular Magnetic Resonance*, 2012; 14(1).
113. Verma A, Solomon SD., Diastolic Dysfunction as a Link Between Hypertension and Heart Failure. *Medical Clinics of North America*, 2009; 93(3) 647-664.
114. Wan SH, Vogel MW, Chen H., Pre-Clinical Diastolic Dysfunction. *Journal of the American College of Cardiology*, 2014; 63(5) 407-416.
115. Gaasch WH, Zile MR., Left Ventricular Diastolic Dysfunction and Diastolic Heart Failure. *Annual Review of Medicine*, 2004; 55. 373-394.
116. Kass DA, Bronzwaer J, Paulus WJ., What Mechanisms Underlie Diastolic Dysfunction in Heart Failure?. *American Heart Association*, 2004; 94(12) 1533-1542.
117. Shah SJ, Kitzman DW, Borlaug BA et al., Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction. *American Heart Association: Circulation*, 2016; 134(1) 73-90.
118. Redfield MM, Jacobsen SJ, Burnett JC et al., Burden of Systolic and Diastolic Ventricular Dysfunction in the Community. *JAMA*, 2003; 289(2)194-202.

119. Chobanian AV, Bakris GL, Black HR et al., Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. ***American Heart Association: Hypertension***, 2003; 42(6)1206-1252.
120. Galderisi M, Petrocelli A, Alfieri A et al., Impact of ambulatory blood pressure on left ventricular diastolic dysfunction in uncomplicated arterial systemic hypertension. ***American Journal of Cardiology***, 1996; 77(8)597-601.
121. Oe Y, Shimbo D, Ishikawa J et al., Alterations in Diastolic Function in Masked Hypertension: Findings from the Masked Hypertension Study. ***American Journal of Hypertension***, 2013; 26(6) 808-815.
122. Kawaji K, Codella N, Prince MR et al., Automated Segmentation of Routine Clinical Cardiac Magnetic Resonance Imaging for Assessment of Left Ventricular Diastolic Dysfunction. ***American Heart Association: Circulation: Cardiovascular Imaging***, 2009; 2(6) 476-484.
123. Levy BI, Ambrosio G, Pries AR et al., Microcirculation in hypertension: a new target for treatment?. ***American Heart Association: Circulation***, 2001; 104. 735-740.
124. Reglin B, Secomb TW, Pries AR., Structural adaptation of microvessel diameters in response to metabolic stimuli: where are the oxygen sensors?. ***American Journal of Physiology: Heart and Circulatory Physiology***, 2009; 297(6) 2206-2219.
125. Bakker EN, Matlung HL, Bonta P et al., Blood flow-dependent arterial remodelling is facilitated by inflammation but directed by vascular tone. ***Cardiovascular Research***, 2008; 78(2) 341-348.
126. Van den Akker J, Schoorl MJ, Bakker EN et al., Small Artery Remodeling: Current Concepts and Questions. ***Journal of Vascular Research***, 2010; 47. 183-202.

127. Mulvany MJ., Small Artery Remodelling in Hypertension. ***Basic & Clinical Pharmacology & Toxicology***, 2012; 110(1) 49-55.
128. Antonios TF, Singer DR, Markandu ND et al., Structural skin capillary rarefaction in essential hypertension. ***Hypertension***, 1999; 33(4) 998-1001.
129. Greene AS, Tonellato PJ, Zhang Z et al., Effect of microvascular rarefaction on tissue oxygen delivery in hypertension. ***American Journal of Physiology***, 1992; 262(5) 1486-1493.
130. Folkow, B., "Structural factor" in primary and secondary hypertension. ***Hypertension***, 1990; 16(1) 89-101.
131. Pries AR, Reglin B, Secomb TW., Structural response of microcirculatory networks to changes in demand: information transfer by shear stress. ***American Journal of Physiology***, 2003; 284. 2204-2212.
132. Oparil S, Acelajado MC, Bakris GL et al., Hypertension. ***Nature Reviews Disease Primers***, 2018; 22.
133. Redheuil A, Yu WC, Wu CO et al., Reduced Ascending Aortic Strain and Distensibility: Earliest Manifestations of Vascular Aging in Humans. ***Hypertension***, 2010; 55(2) 319-326.
134. Malayeri AA, Natori S, Bahrami H et al., Relation of Aortic Wall Thickness and Distensibility to Cardiovascular Risk Factors (from the Multi-Ethnic Study of Atherosclerosis [MESA]). ***The American Journal of Cardiology***, 2008; 102(4) 491-496.
135. Gupta S, Berry JD, Ayers CR et al., Left Ventricular Hypertrophy, Aortic Wall Thickness, and Lifetime Predicted Risk of Cardiovascular Disease: The Dallas Heart Study. ***JACC: Cardiovascular Imaging***, 2010; 3(6) 605-613.

136. Mani V, Muntner P, Gidding SS et al., Cardiovascular magnetic resonance parameters of atherosclerotic plaque burden improve discrimination of prior major adverse cardiovascular events. *Journal of Cardiovascular Magnetic Resonance*, 2019; 11(10), pp. <https://doi.org/10.1186/1532-429X-11-10>.
137. Santos RD, Nasir K., Insights into atherosclerosis from invasive and non-invasive imaging studies: Should we treat subclinical atherosclerosis?. *Atherosclerosis*, 2009; 205(2) 349-356.
138. Cappendijk VC, Kitty BJ, Kessels A et al., Assessment of Human Atherosclerotic Carotid Plaque Components with Multisequence MR Imaging: Initial Experience. *Radiology*, 2009; 234(2) 487-492.
139. Mohiaddin RH, Burman ED, Prasad SK et al., Glagov remodeling of the atherosclerotic aorta demonstrated by cardiovascular magnetic resonance: the CORDA asymptomatic subject plaque assessment research (CASPAR) project. *Journal of Cardiovascular Magnetic Resonance*, 2004; 6(2) 517-525.
140. Corti R, Fuster V, Fayad ZA et al., Lipid lowering by simvastatin induces regression of human atherosclerotic lesions: two years' follow-up by high-resolution noninvasive magnetic resonance imaging. *Circulation*, 2002; 106(23) 2884–2887.
141. Cai J, Hatsukami TS, Ferguson MS et al., Classification of Human Carotid Atherosclerotic Lesions With In Vivo Multicontrast Magnetic Resonance Imaging. *Circulation*, 2002; 106(11) 1368-1373.
142. Toussaint JF, LaMuraglia GM, Southern JF et al., Magnetic resonance images lipid, fibrous, calcified, hemorrhagic, and thrombotic components of human atherosclerosis in vivo. *Circulation*, 1996; 94(5) 932-938.

143. Frydrychowicz A, Stalder FS, Russe MF et al., Three-dimensional analysis of segmental wall shear stress in the aorta by flow-sensitive four-dimensional-MRI. ***Journal of Magnetic Resonance Imaging***, 2009; 30(1) 77-84.
144. Ferreira VM, Piechnik SK, Dall'Armellina E, Karamitsos TD, Francis JM, Choudhury RP, Friedrich MG, Robson MD, Neubauer S. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. ***Journal of Cardiovascular Magnetic Resonance***, 2012 ; 21 (14) 42. doi: 10.1186/1532-429X-14-42.
145. Hoey, E, Pakala V, Teoh J et al., The Role of Imaging in Hypertensive Heart Disease. ***American Heart Association Journals***, 2014; 23. 327.
146. Norton GR, Petersen VR, Robinson C et al., Independent of left ventricular mass, circulating inflammatory markers rather than pressure load are associated with concentric left ventricular remodelling. ***International Journal of Cardiology***, 2019; 274. 342-347.
147. Kuroda K, Kato TS, Amano A., Hypertensive cardiomyopathy: A clinical approach and literature review. ***World Journal of Hypertension***, 2015; 5(2): 41-52.
148. Nadruz, Myocardial remodeling in hypertension. ***Journal of Human Hypertension***, 2015; 29: 1-6.
149. Cuspidi C, Sala C, Negri F et al., Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. ***Journal of Human Hypertension***, 2012; 26: 343-349.

150. Ganau A, Devereux RB, Roman MJ et al., Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. **Journal of the American College of Cardiology**, 1992; 19(7): 1550-1558.
151. Scatteia A, Baritussio A, Bucciarelli-Ducci C., Strain imaging using cardiac magnetic resonance. **Heart Failure Reviews**, 2017; 22: 465-476.
152. Rodrigues JC, Amadu AM, Dastidar AG., 2016. Comprehensive characterisation of hypertensive heart disease left ventricular phenotypes. 2016; 102.
153. Frohlich ED, Apstein C, Chobanian AV, Devereux RB, Dustan HP, Dzau V, Fauad-Tarazi F, Horan MJ, Marcus M, Massie B, Pfeffer MA, Re RN, Roccella EJ, Savage D, Shub C. The heart in hypertension. **N Engl J Med**. 1992; 327:998–1008.
154. Drazner MH. The transition from hypertrophy to failure: how certain are we? **Circulation**. 2005; 112:936–938.
155. Vasan RS, Glazer NL, Felix JF, Lieb W, Wild PS, et al. Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data. **JAMA**. 2009; 302:168–178.
156. Frazer KA, Murray SS, Schork NJ, Topol EJ. Human genetic variation and its contribution to complex traits. **Nat Rev Genet**. 2009; 10:241–251.
157. Sehgal S, Drazner MH. Left ventricular geometry: does shape matter? **Am Heart J**. 2007; 153:153–155.
158. Drazner MH. Left ventricular hypertrophy in special populations. In: , Walsh RA, ed. **Molecular Mechanisms of Cardiac Hypertrophy and Failure**. Abingdon, United Kingdom: Taylor & Francis; 2005:501–512

159. Krumholz HM, Larson M, Levy D. Sex differences in cardiac adaptation to isolated systolic hypertension. **Am J Cardiol.** 1993; 72:310–313
160. Chahal NS, Lim TK, Jain P, Chambers JC, Kooner JS, Senior R. New insights into the relationship of left ventricular geometry and left ventricular mass with cardiac function: a population study of hypertensive subjects. **Eur Heart J.** 2010; 31:588–594.
161. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. **Circ Cardiovasc Imaging.** 2009; 2:191–198.
162. Zabaloitia M, Berning J, Koren MJ, Stoylen A, Nieminen MS, Dahlof B, Devereux RB. Impact of coronary artery disease on left ventricular systolic function and geometry in hypertensive patients with left ventricular hypertrophy (the LIFE study). **Am J Cardiol.** 2001; 88:646–650.
163. Palmieri V, Bella JN, Arnett DK, Liu JE, Oberman A, Schuck MY, Kitzman DW, Hopkins PN, Morgan D, Rao DC, Devereux RB. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. **Circulation.** 2001; 103:102–107
164. Gottdiener JS, Reda DJ, Materson BJ, Massie BM, Notargiacomo A, Hamburger RJ, Williams DW, Henderson WG; the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Importance of obesity, race and age to the cardiac structural and functional effects of hypertension. **J Am Coll Cardiol.** 1994; 24:1492–1498.
165. de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. **Hypertension.** 1994; 23:600–606.

166. Galea N, Carbone I, Cannata D et al., Right ventricular cardiovascular magnetic resonance imaging: normal anatomy and spectrum of pathological findings. **Insights Imaging**, 2013; 4: 213-223.
167. Scully PR, Bastarrika G, Moon JC et al., Myocardial Extracellular Volume Quantification by Cardiovascular Magnetic Resonance and Computed Tomography. **Current Cardiology Reports**, 2018; 20(3): 15.
168. Liao D, Arnett DK, Tyroler HA et al., Arterial Stiffness and the Development of Hypertension. **Hypertension**, 1999; 34(2): 201-206.
169. Dudenbostel T, Acelajado MC, Pisoni R et al., Refractory Hypertension: Evidence of Heightened Sympathetic Activity as a Cause of Antihypertensive Treatment Failure. **Hypertension**, 2015; 66(1): 126-133.
170. Foex P, Sera JW., Hypertension: pathophysiology and treatment. Continuing Education in Anaesthesia, Critical Care & Pain. **British Journal of Anaesthesia**, 2004; 4(3): 98-99.
171. Dharmashankar K, Widlansky ME., Vascular Endothelial Function and Hypertension: Insights and Directions. **Current Hypertension Reports**, 2010; 12(6): 448-455.
172. Kizhakekuttu TJ, Widlansky ME., Natural antioxidants and hypertension: promise and challenges. **Cardiovascular Therapy**, 2010; 28(4): 20-32.
173. Widder J., Endothelium-dependent and -independent vasoreactivity of rat basilar artery in chronic heart failure. **Journal of Cardiovascular Pharmacology**, 2000; 35(4): 515-522.
174. Vanhoutte PM., Endothelium-dependent responses in congestive heart failure. **Journal of Molecular Cell Cardiology**, 1996; 28(11): 2233-2240.

175. Hadi AR, Carr CS, Suwaidi JA., Endothelial Dysfunction: Cardiovascular Risk Factors, Therapy, and Outcome. ***Vascular Health and Risk Management***, 2005; 1(3): 183-198.
176. Bonetti PO, Lerman LO, Lerman A., Endothelial Dysfunction: A marker of atherosclerotic risk. ***Arteriosclerosis, Thrombosis and Vascular Biology***, 2003; 23(2): 168-175.
177. Cohn JN, Duprez DA, Grandits GA., Arterial Elasticity as Part of a Comprehensive Assessment of Cardiovascular Risk and Drug Treatment. ***Hypertension***, 2005; 46(1): 217-220.
178. Calhoun DA, Jones D, Textor S et al., Resistant Hypertension: Diagnosis, Evaluation, and Treatment: A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. ***Circulation***, 2008; 117: 510-526.
179. Messerli FH, Bangalore S, Bavishi C et al., Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use?. ***Journal of the American College of Cardiology***, 2018; 71(13): 1474-1482.
180. Klabunde RE., 2013. Cardiovascular Pharmacology Concepts. [Online] Available at: <https://cvpharmacology.com/vasodilator/alpha> [Accessed 5 June 2019].

## Appendices

1. Similarity index report
2. Consent form
3. CUBIC Patient screening form
4. Ethics approval
5. Ethics renewal

## Appendix 1: Similarity Index Report

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### ORIGINALITY REPORT

<b>11</b> %	<b>8</b> %	<b>12</b> %	<b>2</b> %
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

### PRIMARY SOURCES

<b>1</b>	<a href="http://preview-jcmr-online.biomedcentral.com">preview-jcmr-online.biomedcentral.com</a> Internet Source	<b>4</b> %
<b>2</b>	<a href="http://onlinelibrary.wiley.com">onlinelibrary.wiley.com</a> Internet Source	<b>1</b> %
<b>3</b>	PanVascular Medicine, 2015. Publication	<b>1</b> %
<b>4</b>	<a href="http://www.thieme-connect.de">www.thieme-connect.de</a> Internet Source	<b>1</b> %
<b>5</b>	Mohammed Siddiqui, Tanja Dudenbostel, David A. Calhoun. "Resistant and Refractory Hypertension: Antihypertensive Treatment Resistance vs Treatment Failure", Canadian Journal of Cardiology, 2016 Publication	<b>1</b> %
<b>6</b>	Karaye, Kamilu M., and Aimé Bonny. "Right ventricular dysfunction in systemic hypertension: A call to action", International Journal of Cardiology, 2016. Publication	<b>1</b> %

## Appendix 2: Consent Form and Patient Information Leaflet

### PARTICIPANT INFORMATION SHEET

## Cardiovascular magnetic resonance characterisation of the phenotype of refractory hypertension

You are invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your doctor, if you wish. This leaflet will tell you the purpose of the study, what will happen to you when you take part and gives you detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

### **What is the purpose of the study?**

Patients with refractory hypertension (RHTN) have uncontrolled high blood pressure despite effective maximal treatment and have increased cardiovascular risk compared to patients with easily controlled hypertension. These cardiovascular risk factors include: left ventricular hypertrophy (LVH), chronic kidney disease (CKD) and obstructive sleep apnoea. We would like to identify patients with RHTN and compare phenotypes in these patients to controlled hypertensives and the normal population using cardiovascular MRI (CMR).

If you take part in this study, you will be seen at a visit, where you will be examined and have a resting electrocardiogram (ECG). If you have not had a recent ultrasound scan of the heart, you will be offered one. We will then examine the structure and function of your heart with an MRI scan. Lastly, we will also perform an applanation tonometry test to assess arterial elasticity. You will not be asked to take any additional long-term pill or alter your regular medication in any way.

### **Why have I been invited?**

You have been invited because you have either been previously diagnosed with RHTN or controlled hypertension, or because you have not been diagnosed with RHTN or controlled HTN and have normal BP values.

### **Do I have to take part?**

It is up to you to decide whether or not to take part. If you decide to take part, you are free to withdraw consent at any time without giving a reason. Your decision will not affect the standard of care you receive. If you decide that you no longer wish to continue with the study, we would still retain any data already obtained from you up to the point of your withdrawal.

### **What would happen to me if I take part?**

If you decide to be a participant, you would attend a visit that will last about 2.5 hours. At this visit, we will ask some general questions about your health and regular medication. Next, we will do a brief examination that includes measurement of your pulse, blood pressure, weight and height. An ECG trace of your heart's electrical impulse will be done. After that, we may perform an ultrasound scan of your heart. We will then measure your arterial elasticity using a non-invasive tonometry machine, and lastly we will scan your heart non-invasively using cardiac MRI. If your ultrasound or MRI scan suggests abnormalities, we will advise your doctors to refer you to a cardiologist for review.

Below, all the above-mentioned tests are discussed in a little bit more detail:

#### **a. Clinical assessment**

The assessment will start by asking you a set of questions about your health and previous medical conditions, using a structured questionnaire. The physical exam will include measurement of your pulse, blood pressure, weight and height, as well as an examination of the cardiovascular system.

**b. The heart MRI scan (approximately 60 minutes)**

The MRI scan of your heart will be the most important part of this study. MRI scans are painless but involve the use of a strong magnetic field, so if you have any of the following, you would not be suitable for a scan, and would not be able to take part in this study:

- a permanent pacemaker
- metal clips in blood vessels of the brain
- an injury to the eye involving fragments of metal
- insulin pump
- shrapnel injuries
- other metal or electronic implants affected by the magnetic field
- neurostimulators
- cochlear implant

The MRI scanner is shaped like a polo mint, the hole inside measuring about 70 centimeters wide, with a table that slides in and out. You will be asked to change into a hospital gown and to lie still on your back on the table, while your heart is scanned. You will also be asked to breathe in and out and hold your breath for several seconds for some of the scans. Pictures of the heart are created using a magnetic field, radio waves and computers. When images are being taken, the MRI scanner makes a loud noise, and you will be provided with earphones to protect your ears. It is important that you lie still for the duration of the scan.



To evaluate fully the blood circulation and your heart muscle for inflammation and scarring and tissue characteristics we shall inject some contrast dye, called gadolinium, through a drip in your arm.

**c. The ECG (5 minutes)**

We will take an electrocardiogram (ECG) of your heart. An ECG is a tool that uses surface electrodes on certain points on your chest and arms to monitor the electrical properties of your heart.

**d. The ultrasound of the heart (60 minutes)**

An echocardiogram or ultrasound of your heart is a safe and painless procedure to study heart structure and function. You will be asked to lie on a couch on your left side, and a probe will be placed on your chest. Lubricating jelly is used so the probe makes good contact with the skin.

Ultrasound waves then create images of your heart on the scanner monitor. It normally takes 15-20 minutes to acquire these images.

**e. The applanation tonometry (30 min)**

This is a safe, non-invasive test that measures arterial elasticity by assessing central blood pressure as a more accurate method of determining cardiovascular disease risk. You will be asked to lie down comfortably as a blood pressure cuff is placed on your non-dominant arm. While your blood pressure is being recorded, a wrist stabilizer will be placed on your dominant hand with the arterial sensor on your wrist where your pulse is the strongest, this will allow the sensor to capture your BP waveform for analysis. It takes approximately an hour to perform three sets of measures on this test.

**What about travel expenses?**

We will reimburse travel expenses to and from the hospital. Lunch will be provided or reimbursed.

**What will I have to do, if I agree to take part in this study?**

Attend a visit at Groote Schuur Hospital for the assessment, blood tests and for the scans.

Consent to taking part in this study by signing a form.

We will ask that you do not have anything to eat the 4-6 hours before the visit.

Undergo the procedures as described above.

**Are there any other possible risks from taking part?**

The scanning is done using an MRI scanner which is also used routinely in clinical practice to acquire images of various body parts. MRI scans are safe, non-invasive and do not involve any ionising radiation (X-rays). Some people find the space limitation in the scanner uncomfortable, but you will be given a chance to see the scanner to make sure that you are comfortable in it before the study starts. If you suffer from claustrophobia, it may not be a good idea to participate. The scan is noisy and we will provide headphones to protect your ears. The whole time that you are in the scanner you will be given a buzzer which you will be able to use at any time if you wish to stop the study. As the scanner consists of a powerful magnet, it may attract certain metallic objects. You must not have a scan if you have had metallic objects or medical devices (e.g. pacemaker) inserted into your body during an operation. While MRI is safe in pregnancy, because this is a research study, as a precaution we advise you to tell us if there is any chance you might be pregnant. The doctor or radiographer will go through a list of possible risks with you before you go into the scanner.

In the unlikely event of us seeing any structural abnormalities on your MRI scan, a member of our research team will discuss the implications with you and, with your permission, your doctor may be notified. However, it is important to note that we do not carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a clinical appointment. Rather, our scans are intended for research purposes only. Some people find having a drip in their arm uncomfortable and there can be bruising at the site of needle entry. Our staff is trained in drip insertion and we will make sure you are as comfortable as possible.

Gadolinium, the dye used for the MRI scans, has been in clinical use for over 20 years. As the dye is being injected, some people report a sensation of warmth at the injection site. It is unusual to feel pain, and in this case, we would stop the injection immediately. Rarely, some people feel slightly nauseous or have a metallic taste following the injection, but vomiting is exceedingly rare. Occasionally, people have developed a rash; however, severe allergic reactions are very rarely. Again, this dye is injected through a drip in the arm. There is no pain associated with the injection at the site. There is a small risk of an allergic reaction to the dye.

Tonometry, ECG and ultrasound are safe, non-invasive tests, with no known serious risks/harm. Rarely, individuals having either test may develop an allergic reaction to placement of electrodes that results in a mild rash. This rash disappears in a few days without any treatment.

It is important to note that in a large-volume MRI center like Groote Schuur Hospital, where our experienced staff has been doing MRI scans for many years, the risk of harm from the MRI and other tests is exceedingly small.

**What are the possible benefits?**

There is no direct benefit for you as an individual taking part in this study. We hope that by studying people with your condition using cardiac MRI, we may be able to improve understanding of this condition and help to inform screening/treatment of future patients.

**What happens when the research study stops?**

The end of the study will not affect the care you receive from your doctors. The end of the study will mark the official end of your participation in this project. Copies of any publications connected to this study will be available on request from Dr Ntusi and Miss Letuka.

**Will my taking part in the study be kept confidential?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. If you take part in the study, some of the data collected from the study would be looked at by authorised persons from the University of Cape Town, to check that the study is being carried out correctly. All investigators have a duty of confidentiality to you as a research participant, and nothing that could reveal your identity would be disclosed outside the research site. The data collected from the study will be recorded anonymously and you would not be identifiable from this.

The information recorded will be analysed, combined and published anonymously in scientific journals. The Research Committee of the University of Cape Town may review the results as a regulatory body. A clinical protocol of the research was submitted and approved by an ethics committee which is registered by the National Health Research Ethics Council and the University of Cape Town Research Ethics Committee. The research structure ethical principles are in accordance with the World Medical Association Declaration of Helsinki 2013 and Guidelines on Clinical Trials and Ethics in Health Research published by Department of Health.

**What if relevant new information becomes available?**

Sometimes, we (the study investigators) get new information about the procedures being studied. If this happens, one of us will tell you and discuss whether you should continue in the study. If there is sufficient evidence to suggest you may be harmed from participating in this study, the study could be stopped.

**Unexpected findings on your scan**

In the unlikely event of us seeing any structural abnormalities on your MRI scan, a designated clinical specialist will discuss the implications with you and may arrange for further investigations as necessary. However, it is important to note that we do not carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a clinical appointment. Rather, our scans are intended for research purposes only. So if we find anything unusual, it would be appropriate for us to contact your GP/specialist so that they can arrange on-going clinical care for you. But we would only do this after we and the specialist had discussed your options and gained your permission.

**What will happen if I don't want to carry on with the study?**

You are free to withdraw from the study at any time. Anonymised data will be kept till the point you choose to end your participation in the study. Data collected till the point of your withdrawal will be included in the analysis.

**What will happen to the results of the research study?**

We anticipate that the results will be published in a scientific journal for the benefit of the wider medical community. However, individual patients will not be identified in any publication and your personal and clinical details will remain strictly confidential. Any scientific publications arising from

the study will be available on request to all participants. You would have no legal right to a share of any profits that may arise from the research.

**Will your test results be shared with you?**

We will show you the images we acquire from the ultrasound and MRI scans when we finish performing the scans. The results of the other tests will only be available on publication of the results. If however, results of any of any of the tests are grossly abnormal, we will contact you to discuss these with you before suggesting a course of action and contacting your doctor/specialist.

**Who is organising and funding the research?**

The study is organised and conducted by researchers from the University of Cape Town and Groote Schuur Hospital. The studies are funded, in part, by a grant from the National Research Foundation of South Africa.

**Who has reviewed the study?**

The University of Cape Town Human Research Ethics Committee has reviewed and approved the study.

**Insurance and financial arrangements**

Study doctors are covered by insurance. UCT has a no fault insurance policy for trial related injuries which states:

“UCT undertakes that in the event of you suffering any significant deterioration in health or well-being, or from any unexpected sensitivity or toxicity that is caused by your participation in the study it will provide immediate medical care. UCT has appropriate insurance cover to provide prompt payment of compensation for any trial-related injury according to the guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991. Broadly-speaking, the ABPI guidelines recommend that the insured company (UCT), without legal commitment, should compensate you without you having to prove that UCT is at fault. An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request”

**Further information and contact details**

Should you wish to know more about any aspects of this study, please contact Prof Ntusi at 021 406 6200 or alternatively contact Miss Pheletso Letuka at 021 406 6840. You can also contact either one of us via email: Prof Ntusi- [ntobeko.ntusi@uct.ac.za](mailto:ntobeko.ntusi@uct.ac.za) , Miss Pheletso Letuka- [LTKPHE001@myuct.ac.za](mailto:LTKPHE001@myuct.ac.za)

Should you have any concerns regarding your rights or welfare as a research participant, please contact the Faculty of Health Sciences Research Ethics Committee at 021 406 6626 or visit their office at Groote Schuur Hospital, Old main building, E53, room 46, Observatory 7925.

CONSENT FORM

<b>Study Full Title</b>	CMR TO STUDY THE PHENOTYPE OF PATIENTS WITH REFRACTORY HYPERTENSION
<b>Patient ID</b>	
<b>Principal investigator</b>	Prof Ntobeko Ntusi
<b>Co-supervisor</b>	Prof Brian Rayner
<b>Researcher</b>	Miss Pheletso Letuka

	I agree	I disagree
I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	<input type="checkbox"/>	<input type="checkbox"/>
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	<input type="checkbox"/>	<input type="checkbox"/>
I understand that relevant sections of my medical notes and data collected during the study may be looked at by authorized individuals from the University of Cape Town, where it is relevant to my taking part in this research.	<input type="checkbox"/>	<input type="checkbox"/>
I understand that my doctor will, with my permission, be informed of the results of medical tests performed as part of the research, which are important for my health care.	<input type="checkbox"/>	<input type="checkbox"/>
I also understand that I may be invited to return for a second MRI scan, which is optional.	<input type="checkbox"/>	<input type="checkbox"/>
I agree to being contacted in the future to ask if I am interested in future related studies.	<input type="checkbox"/>	<input type="checkbox"/>

CERTIFICATE OF CONSENT

I have read the information letter, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study

Print Name of Participant \_\_\_\_\_

Signature of Participant \_\_\_\_\_

Date \_\_\_\_\_

Day/      Month/      Year

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness \_\_\_\_\_

Thumb print of witness \_\_\_\_\_

Signature of witness \_\_\_\_\_

Date \_\_\_\_\_

Day/      Month / Year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the study that is going to be done. I confirm that the participant was given an opportunity to ask questions about the study. All questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent and the consent has been given freely and voluntarily.

A copy of the Informed consent has been provided to the participant.

Print Name of Researcher/ person taking the consent \_\_\_\_\_

Signature of Researcher/ person taking the consent \_\_\_\_\_

Date \_\_\_\_\_

Day/ Month / Year

**NB: PLEASE KEEP THIS FORM ON A SAFE AND SECURE PLACE**

**Appendix 3: CUBIC Patient screening form**  
**Cape Universities Body Imaging Centre (CUBIC)**  
**University of Cape Town**  
**MRI Patient Screening Form**

Patient Name:	_____		
Hospital/Clinic:	_____		
Date Of Birth:	_____	Weight:	_____
		Height:	_____

**The following information is very important to ensure your safety and to prevent any interference during the MR procedure.**

Please answer the following questions (mark with a X):

		Yes	No	Don't Know
1.	Do you have a cardiac pacemaker/defibrillator?			
2.	Do you have a neuro-stimulator?			
3.	Do you have a cochlea implant/surgery to your ears? (If yes, please specify)			
4.	Have you ever had heart surgery such as a valve replacement? (If yes, please specify)			
5.	Have you ever had any type of electronic, mechanical, or magnetic implant? (If yes, please specify)			
6.	Do you have any foreign body in your eyes or body? (Bullet fragments etc..)			
7.	Do you have a vena cava filter?			
8.	Do you have a prosthetic limb, eye or other artificial device not already mentioned? (If yes, please specify)			
9.	Are you pregnant or breast feeding?			
10.	Are you claustrophobic?			
11.	Do you have aneurism clips?			
12.	Do you have renal impairment?			
13.	Do you have asthma?			
14.	Do you have allergies? (If yes, please specify)			
15.	Do you have any other implants? (e.g. screws, plates, joint replacements)			
18.	Other			

I hereby acknowledge that the potential risks of the examination have been explained to me and that during the course of the investigation it may for the intravenous injection of a contrast agent.

Attention: It is the policy of this institution not to discuss results of the MR Investigation with the patients for ethical reasons. All enquiries in this regard should be directed to the referring physician.

**Patient Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Consented by:** \_\_\_\_\_

*Please remove all loose metallic objects, including metallic body piercings, hearing aids and dentures.*

## Appendix 4: Ethics Approval



UNIVERSITY OF CAPE TOWN  
Faculty of Health Sciences  
Human Research Ethics Committee



Room E53-24 Old Main Building  
Groote Schuur Hospital  
Observatory 7925  
Telephone [021] 404 7682 • Facsimile [021] 406 6411  
Email: [prol.basma@uct.ac.za](mailto:prol.basma@uct.ac.za)  
Website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms)

14 July 2017

**HREC REF: 494/2017**

**Prof N Ntusi**  
Medicine Dept  
346.53  
Old Main Building

Dear Prof Ntusi

**PROJECT TITLE: CARDIOVASCULAR MAGNETIC RESONANCE CHARACTERISATION OF THE PHENOTYPE OF REFRACTORY HYPERTENSION (MSc Candidate - P Letuka)**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study. This is subject to adding the UCT no fault insurance clause to the informed consent document.

**Approval is granted for one year until the 30th July 2018.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: [www.health.uct.ac.za/fhs/research/humanethics/forms](http://www.health.uct.ac.za/fhs/research/humanethics/forms))

*We acknowledge that the student Pheletso Letuka will be involved in this study.*

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

**Please quote the HREC REF in all your correspondence.**

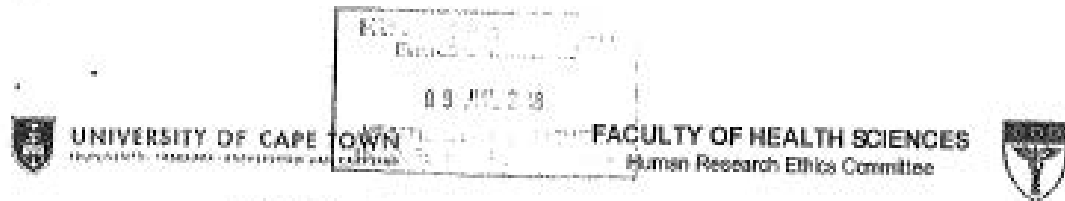
Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

Signature removed to avoid exposure online

**PROFESSOR M BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**  
Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938

## Appendix 5: Ethics Renewal



### FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until next renewal date:	30/07/2019
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC	Signature removed	Date Signed	9/7/2018

Comments to PI from the HREC

Principal Investigator to complete the following:

#### 1. Protocol information

Date (when submitting this form)	09 July 2018		
HREC REF Number	494/2017	Current Ethics Approval was granted until	30 July 2018
Protocol title	Cardiovascular magnetic resonance characterization of the phenotype of refractory hypertension		
Protocol number (if applicable)	N/A		
Are there any sub-studies linked to this study?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.	N/A		
Principal Investigator	Mabeko Ntusi		
Department/ Office Internal Mail Address	Division of Cardiology, Department of Medicine, University of Cape Town J46.53, Old Main Building, Groote Schuur Hospital Anzio Road, Observatory, 7925		