DETERMINANTS OF LEFT VENTRICULAR HYPERTROPHY AND ITS REGRESSION IN PEOPLE OF AFRICAN ANCESTRY IN SOUTH AFRICA

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ABSTRACT

There is substantial evidence to suggest that independent of conventional BP, LV mass (LVM) is higher in African-Americans than in European-Americans a difference that may translate into a higher prevalence of cardiovascular diseases. In the present thesis I assessed whether LVM is similarly elevated in groups of African descent living in Africa, and subsequently whether 24-hour, day or night BP or indices of arterial stiffness could explain the variability in LVM beyond conventional BP in this population group. As there is considerable controversy as to whether 24-hour BP measurements are better predictors of the regression of LVH than conventional BP and whether antihypertensive agents that target the renin-angiotensin system (RAS) regress LV hypertrophy (LVH) independent of BP in groups of African descent, in the present thesis I therefore also assessed these questions.

In 141 healthy adult participants obtained from a random sample of nuclear families (n=399) of African ancestry living in Soweto, I determined that LVM adjusted for body surface area to the first power was an appropriate allometric signal to account for growth effects on LVM. The allometric signals established in other populations considerably over-adjusted for LVM in the group that I studied with marked negative relations noted. After adjusting for body surface area I noted upper thresholds of LVM index (LVMI) of 134 g/m^2 for men and 112 g/m^2 for women. As compared to thresholds described for other population samples these thresholds were noted to be modestly higher.

In 187 women from randomly recruited nuclear families of African ancestry, after appropriate adjustments, conventional BP was as closely associated with LVMI as 24-hour BP, and daytime BP was as closely associated with LVMI as night-time BP in women. However, in 110 men from randomly recruited nuclear families of African ancestry, after appropriate adjustments, only night-time BP was associated with LVMI, an effect that was independent of conventional BP ($r=0.21$, $p<0.05$). Indices of nocturnal decreases in BP were not associated with LVMI in either gender group. Furthermore, in

randomly recruited nuclear families of African ancestry, after appropriate adjustments, including systolic BP or pulse pressure, pulse wave velocity (an index of arterial stiffness assessed using applanation tonometry) was independently associated with LVMI in women (n=204, r=0.25, p<0.0005), but not in men (n=123, r=-0.07).

In 173 hypertensive patients of African descent of whom 64 were previously untreated and 109 were previously treated, I assessed whether ambulatory BP is a better predictor of on-treatment decreases in LVMI over a 4 month treatment period. In the previously untreated patients, the regression in LVMI correlated to a similar degree (p<0.09) with decreases in conventional (r=0.34; p<0.005) and 24-hour (r=0.26; p<0.04) systolic BP. In this same study sample followed prospectively for 25 months, accounting for effects on ambulatory BP at each time point, the use of the angiotensin-converting enzyme inhibitor, enalapril, was not associated with LVMI, whereas, on-treatment conventional systolic BP (p=0.01) and night-time systolic BP (p=0.01) were associated with LVMI.

In a further study conducted in 87 patients of African ancestry with hypertension and LVH, I showed that changes in systolic ambulatory BP (daytime, r=0.46, p=0.006) were predictive of changes in LVMI after 2 months of treatment with an angiotensin II receptor blocker (candesartan), ACE-I (ramipril) and the diuretic agent, hydrochlorothiazide. Moreover, in a final study I showed that in hypertensive patients of African ancestry, initiating therapy with the diuretic, indapamide SR and then adding the ACE-I, perindopril 4 mg (n=42), was equally as effective as amlodipine (calcium channel blocker) (n=44) therapy at reducing ambulatory BP and LVMI.

Thus, in conclusion, groups of African descent living in Africa have only marginally higher thresholds for LVM than other population groups. Moreover, in this population group, nocturnal BP has a conventional BP-independent effect on LVMI in men, but not in women, whereas arterial stiffness has a conventional BP-independent effect on LVMI in women, but not in men. Further, in this population, reductions in LVM produced by antihypertensive therapy appear to be equally as closely related to

conventional as ambulatory BP and in contrast to findings in groups of European ancestry, where RAS blockers produce unique benefits on LVM beyond conventional BP reductions, in groups of African ancestry in Africa, RAS blockers produce no BP-independent reductions in LVM. Moreover, in this population, decreases in LVM in patients with LVH produced by RAS blockers are related to ambulatory BP changes and despite the ineffectiveness of RAS blockers on BP when used as monotherapy in this population, RAS blockers together with diuretics are equally as effective in decreasing BP and LVM as compared to a class of antihypertensive agents with established efficacy (calcium channel blockers). Hence when compelling indications for RAS blockade exist, RAS blocker-diuretic combinations are effective therapy in patients of African descent living in Africa.

DECLARATION

I declare that this thesis is my own, unaided work. It is being submitted for the degree of Doctor of Philosophy in the Faculty of Medicine, University of the Witwatersrand, Johannesburg. The work contained in this thesis has not been submitted for any degree or examination in this university, or any other university.

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Elena Neustadt Libhaber

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I certify that the studies contained in this thesis have the approval of the Committee for Research in Human Subjects of the University of the Witwatersrand, Johannesburg. The ethics numbers are: M02-04-72, and M07-07-07 (which incorporates the original numbers M940106, M980206, 000303).

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GAVIN R. NORTON (Supervisor)

TABLE OF CONTENTS

Page

DEDICATION

This thesis is dedicated to my husband Carlos, my children Ariel and Dana, my sister Nora, my parents Max and Edith Neustadt and to my beloved grandmother Gertrude Wang, who taught me to achieve the best I can, no matter what the obstacles.

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STATEMENT OF CONTRIBUTION TO WORK

The studies described in this thesis were designed by myself in consultation with my supervisor. To ensure appropriate measurements, the echocardiography was performed by an experienced echocardiographer and cardiologist assisted by myself in all cases. The quality control and additional measurements were performed in-part by myself together with assistance from clinical nurses and trained technicians under my supervision. The database management, cleaning of the data, data analysis and data interpretation were all done by myself.

LIST OF ABBREVIATIONS

ABP: ambulatory blood pressure

ACE: angiotensin-converting enzyme

ACE-I: angiotensin-converting enzyme inhibitor

ACE-Is: angiotensin-converting enzyme inhibitors

AI: augmentation index

AIc: central augmentation index

A II: angiotensin II

AIp: peripheral augmentation index

ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

ANOVA: analysis of variance

APOGH: African Study of Genes in Hypertension

ARIC: Atherosclerosis Risk in Communities

BMI: body mass index

BP: blood pressure

BSA: body surface area

CARDIA: Coronary Artery Risk Development in Young Adults

CCB: Calcium channel blocker

CCBs: calcium channel blockers

CHF: congestive heart failure

CHS: Cardiovascular Health Study

CI: confidence interval

CV: cardiovascular

CVD: cardiovascular diseases

d 24: changes in 24-hour

d Con: conventional techniques

d Din: dinamap

DADBP: mean daytime ambulatory diastolic BP

DBP: diastolic blood pressure

DM: diabetes mellitus

ECG: electrocardiogram

EF: ejection fraction

FS: fractional shortening

FSH: follicular stimulant hormone

GITS: gastrointestinal therapeutic system

HbA1c: glycosylated hemoglobin

HCTZ: hydrochlorothiazide

HDL: high density lipids

IHD: ischaemic heart disease

IVS: inter-ventricular septal wall thickness

JNC7: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure

LDL: low density lipids

LIFE: Losartan Intervention for Endpoint Reduction in Hypertension

LV: left ventricular

LVED: left ventricular end diastolic

LVEDD: left ventricular end diastolic diameter

LVEF: left ventricular ejection fraction

LVESD: left ventricular end systolic diameter

LVH: left ventricular hypertrophy

LVM: left ventricular mass

LVMI: left ventricular mass index

MAVI: Massa Ventricolare sinistra nell' Ipetersione arteriosa

MI: myocardial infarction

MWT: end-diastolic mean wall thickness

NHANES: National Health and Nutrition Examination Surveys

NHSL: South African National Health Systems Laboratories

od or o/d: once daily

PAMELA: Pressione Arteriose Monitorate E Loro Associazioni

PP: pulse pressure

PRESERVE: Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement

PVD: peripheral vascular diseases

PWED: posterior ventricular wall thickness

PWT: posterior wall thickness

PWV: pulse wave velocity

RAS: renin-angiotensin system

r: correlation coefficient

RWT: relative wall thickness

SAMPLE: Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation

SBP/DBP: systolic BP/diastolic BP

SBP: systolic blood pressure

SES: socioeconomic status

SOWETO: South Western township

SR: slow release

TG: triglycerides

USA: United States of America

LIST OF TABLES

Chapter 6:

Chapter 7:

Chapter 8:

LIST OF FIGURES

Chapter 2:

Chapter 3:

Chapter 4:

Chapter 5:

Chapter 7:

Chapter 8:

PREFACE

Left ventricular hypertrophy (LVH) is recognised as a risk factor of cardiovascular morbidity and mortality independent of conventional blood pressure (BP) in populations of Caucasian and African origins. Moreover, there is now compelling evidence to indicate that LV mass (LVM) is increased in African as compared to European Americans, an effect that is independent of conventional BP. However, the mechanisms responsible for conventional BP-independent ethnic differences in LVM have not been determined, but may relate to ethnic differences in 24-hour BP profiles or to arterial stiffness. These questions prompted me to assess whether, as compared to other population samples, thresholds for LVM are greater in a group of healthy individuals recruited in large randomly selected population of African descent living in Africa. Further, I assessed whether either ambulatory BP or an index of arterial stiffness (pulse wave velocity) predict LVM better than or independent of conventional BP in this population sample and whether ambulatory BP is a better predictor of on-treatment regression of LVM than conventional BP in hypertensive patients of African ancestry. These studies are described in chapters 2-5 of the present thesis.

Although in groups of European descent the use of blockers of the renin-angiotensin system (RAS) regress LVH beyond BP effects, current thinking is that this effect may not occur in groups of African descent. This prompted me to assess, in a ~2 year study described in chapter 6, whether the use of an angiotensin-converting enzyme inhibitor was associated with changes in LVM beyond ambulatory BP in hypertensives of African ancestry. Moreover, in a further study described in chapter 7 I assessed whether there is indeed an association between the regression of LVH and ambulatory BP in hypertensives of African descent. Last, as there are compelling indications for the use of RAS blockers, including the presence of LVH, but calcium channel blockers are far more effective antihypertensive agents in hypertensives of African ancestry than RAS blockers, I assessed whether a diuretic/ACE-I combination was as effective as a calcium

channel blocker at decreasing ambulatory BP and LVM in hypertensives of African ancestry. These data are described in chapter 9.

In this thesis I have first reviewed the scientific literature that relates to LVM and LVH with a specific focus on what is known about LVM in groups of African descent. This review is the content of chapter 1 and is meant to lead the reader through a series of arguments that support the hypotheses tested in this thesis. At the end of chapter 1 I list the aims of the thesis. Chapters 2-8 consist of semi-independent chapters, each divided into an “abstract”, “introduction”, “methods”, “results” and “discussion” sections. Although these chapters are separated from each other as they deal with specific hypotheses, there is overlap between chapters and the progression of arguments from chapter-to-chapter has been underscored.

In support of this thesis I am either first author or a co-author on three papers published to-date (Skudicky, Sareli, Libhaber et al, Circulation 2002;105:830-836, Libhaber et al Am J Hypertens 2004;17:5,428-443 and Libhaber et al, Journal of Human Hypertension 2005;19:959-961) and a number of papers that are presently being prepared for publication. In addition other components of this thesis have been presented at international congresses (Libhaber et al 21st Annual Scientific Meeting of the American Society of Hypertension. May 16-18, 2006 New York. USA, Libhaber et al. World Congress of Cardiology 2006. September 2-6 2006. Barcelona. Spain).

Chapter 1

INTRODUCTION

Left ventricular hypertrophy: Current knowledge, controversies and outstanding issues with particular reference to persons of African descent

1.0 Introduction

Cardiovascular (CV) diseases (CVD) including strokes, myocardial infarction (MI), renal failure, heart failure, sudden cardiac death and peripheral vascular disease (PVD), share similar risk factors. Cardiovascular diseases are amongst the leading causes of death in adults in both developed (reviewed by guidelines committees including World Health Organization, International Society of Hypertension Writing Group. [Whitworth 2003]; European Society of Hypertension-European Society of Cardiology Guidelines Committee 2003; Chobanian et al 2003; Williams et al 2004) and developing (Kahn et al 1999) countries. A significant proportion of the risk of developing CVD is attributed to hypertension, smoking, diabetes mellitus, dyslipidaemias, aging and excess adiposity (reviewed by guidelines committees including World Health Organization, International Society of Hypertension Writing Group. [Whitworth 2003]; European Society of Hypertension-European Society of Cardiology Guidelines Committee 2003; Chobanian et al 2003; Williams et al 2004). In the present thesis I have studied one of the principle risk factors for CVD in groups of African descent, namely hypertension. The main aim of the present thesis was to attempt to clarify some of the outstanding issues that relate to the development and regression of a target organ change in hypertension, namely left ventricular hypertrophy (LVH), in groups of African descent. As will be underscored the identification of LVH is of major clinical importance in any population group. However, the factors that drive the development of LVH and its changes with therapy still remain uncertain. This is particularly obscure in groups of African descent.

1.1 The prevalence of hypertension in groups of African ancestry

With respect to pathological LVH, its prevalence is generally perceived to depend on the prevalence of hypertension and excess adiposity. Consequently, it is first worth considering epidemiological issues that relate to hypertension prevalence in groups of

African descent. Importantly, the prevalence of hypertension in non-African countries has previously been reported to be twice as high in black as compared to Caucasian communities (Comstock 1957, Stamler et al 1975, Meade et al, 1978, Chaturvedi et al 1993), a difference that still persists despite a better awareness and treatment of the condition, Indeed, the latest analysis of the National Health and Nutrition Examination Surveys (NHANES) in the United States of America (USA) indicates that the prevalence of hypertension in those of African descent is 40.5% as compared to 27.4% in those of European descent (Glover et al 2005). These are quite extraordinary differences and represent an increasing rather than decreasing difference in prevalence than that previously reported on (Ashaye and Giles, 2003). Yet more and not less hypertensives of African than European descent in the USA are aware of their condition (70.3 vs 62.9%) and at least the same proportion have blood pressures (BP) controlled to target levels (29.8 vs 29.8%)(Glover et al 2005). Even in the context of equivalent health promotion services between ethnic groups, subjects of African ancestry between the ages of 45-to-64 years are still 5.6 times more likely to be hospitalised for hypertension than their Caucasian counterparts (Holmes et al 2005). Moreover, higher prevalence rates of hypertension persist in those of African descent in the USA when adjusting for income and educational level (Howard et al 2000). Thus, under conditions of equivalent care, awareness, income and education, the higher prevalence rates of hypertension in individuals of African descent are sustained. In South Africa about one-fifth to one-quarter of groups of African descent have hypertension and a large proportion of these subjects have BPs that are not at target levels (Steyn et al 1996; Steyn et al 2001; Alberts et al 2005).

1.2 Cardiovascular disease in groups of African descent: Hypertension as a major risk factor

As a consequence of the high prevalence of hypertension in groups of African descent, there is inevitably an increased risk for CVD. Indeed, in developed countries there is a greater prevalence of some CVD in ethnic groups of African origins. In the USA, the prevalence of strokes is greatest amongst groups of African origins (Gillum 1999; Hollar et al 2004; McGruder et al 2004; Jamerson 2004; Howard 2001, Sacco et al 2001). In developing countries in Africa, there is some evidence to indicate that stroke is highly prevalent in rural communities (Seedat et al 1998, Connor et al 2006) and presumably also in urban communities. Although until recently ischaemic heart disease (IHD) was thought to be a rare entity in sub-Saharan Africa, based on hospital admissions, the prevalence is thought to be increasing at a dramatic level. Moreover, the risk of coronary artery disease may be just as high in patients of African ancestry with stroke as it is in patients of European ancestry with stroke (Joubert et al 2000). As stroke is a common cause of morbidity and mortality in sub-Saharan Africa it may therefore be argued that IHD is also common in these countries, but that it goes largely undetected or is not expressed as an important clinical phenotype. However, true prevalence data for IHD in these countries has yet to be reported on.

1.3 Left ventricular hypertrophy in risk stratification: Outstanding issues still remain

In the management of hypertension, to predict the risk for stroke and other CV events, it is now widely acknowledged that identifying target organ damage, such as LVH, is important in risk stratification (see section 2.1 below) (reviewed by guidelines committees including World Health Organization, International Society of Hypertension Writing Group. [Whitworth 2003]; European Society of Hypertension-European Society of

Cardiology Guidelines Committee 2003; Chobanian et al 2003; Williams et al 2004). Moreover, a therapeutic aim of antihypertensive therapy is to regress LVH (see section 2.4 below). However, with respect to LVH, there are many questions that remain unanswered, and of particular importance to countries like South Africa there are ethnic differences in LV mass (LVM) reported in non-African countries, with higher LVM values noted in groups of African descent (Drazner et al 2005) (also see section 3.0 below). Moreover, there are data that indicate important ethnic differences in the response of LVM to antihypertensive agents (see section 5.2 below). Yet the clinical relevance of these ethnic differences remains uncertain.

The ethnic difference in LVM in groups of African as opposed to European descent (Drazner et al 2005) has largely been attributed to the well recognized relationship between BP and LVM. In other words, the greater prevalence of hypertension in groups of African ancestry would predictably translate into more target organ changes. However, even after adjusting for conventional BP values, groups of African ancestry appear to have a higher LVM (Drazner et al 2005, see section 3.0 below). Moreover, conventional BP accounts for a relatively small portion of the variability in LVM in any population (see section 4.1 below). Thus the mechanisms that explain ethnic differences in LVM or remodeling and differences in response to therapy have not been entirely resolved. The purpose of this thesis was therefore in-part to attempt to ascertain whether LVM is indeed particularly high in groups of African descent living in Africa, and if so to identify any unique characteristics of the factors that may explain LVM in this group. Moreover, an additional purpose of this thesis was to further understand the potential ethnic differences in therapeutic responses of the LV to antihypertensive therapy.

In this chapter I will therefore review the evidence to support the notion that LVM and its regression predicts CV events in Caucasians and groups of African descent. I will subsequently attempt to explain the relationship between LVM and adverse CV outcomes. I will then summarize the evidence to indicate that persons of African ancestry

have a higher LVM. I will also discuss the mechanisms that explain increases in LVM in any population and whether the characteristics of any one of these mechanisms could contribute toward the higher prevalence of an increased LVM in groups of African descent. I will further highlight the apparent ethnic disparities in the BP and LVM responses to antihypertensive therapy and indicate the unresolved issues in this regard.

2.0 Left ventricular hypertrophy: Compensatory change or cardiovascular risk factor?

For many years LVH was considered a compensatory response to a chronic pressure load on the LV. In accordance with the law of Laplace, where wall tension (stress) is proportional to the product of pressure and internal radius and inversely proportional to wall thickness, an increased wall thickness in LVH maintains a normal LV wall stress in the face of increments in pressure generated within the LV cavity. Based on the principle that LV geometry and wall thickness change to maintain systolic stress within normal limits (Grossman et al 1975), LVH was considered an adaptive reaction to a pressure overload with a more favorable outcome predicted (Grossman et al 1975, Gaash et al 1978). However, LVH can no longer be considered a compensatory change. Indeed, epidemiological data indicate that LV mass (LVM) is an independent risk factor for CV events, including MI, stroke, congestive heart failure, sudden cardiac death, renal failure and peripheral vascular disease. The following outlines the evidence to support this notion.

2.1 Left ventricular hypertrophy predicts cardiovascular risk independent of conventional BP in Caucasian populations

Many studies now support the notion that LVH is a predictor of CV risk independent of conventional BP measurerments (Casale et al 1986, Levy et al 1990,

Levy et al 1994, Verdecchia et al 1996, Ghali et al 1998, Gardin et al 2001, Verdecchia et al 2001, Drazner et al 2004). In the Framingham Heart study conducted largely in a Caucasian population, LVM corrected for height was associated with the incidence of death from CVD with a higher relative risk noted in women than in men after adjusting for treatment for hypertension (Levy et al 1990). Even in the absence of arterial hypertension, LVM in Caucasian groups is an independent risk factor for CV events (Gardin et al 2001). In the Italian Multicenter and Prospective Study (Massa Ventricolare sinistra nell' Ipertensione arteriosa) (MAVI) conducted in a largely Caucasian population with essential hypertension, irrespective of baseline conventional BP and treatment for hypertension, the presence of LVH doubled the risk for CV events such as cardiac death, MI, stroke, transient ischemic attack, heart failure, unstable angina, arterial occlusive disease and renal failure (Verdecchia et al 2001). Even after adjusting for other traditional CV risk factors (age, diabetes mellitus and smoking), the CV risk of an increased LVM persisted (Verdecchia et al 2001). In a cohort of Caucasians of the Cardiovascular Health Study (CHS) followed for 5 years, LVH was also associated with a decrease in left ventricular ejection fraction (LVEF) or diastolic function independent of traditional risk factors including conventional BP (Drazner et al 2004). Thus, LVH predicts the transition to cardiac dysfunction.

The conventional BP-independent relationship between LVM/LVH and CV outcomes is perhaps not surprising as an occasional conventional BP measurement may not predict actual BP changes over a prolonged period. Indeed, even over a 24-hour period, BP varies considerably over time (Mancia et al 1999). Thus, LVM and hence CV risk could be the product of BP over a prolonged period. If this argument holds, then it should be obvious that LVM would be a better predictor of CV events than the occasional BP measurement. As an extension to this argument, it may also be argued that during antihypertensive therapy, measurements of BP over prolonged time periods, rather than an occasional conventional BP measurement should predict CV events equally as well

as changes in LVM over time. However, as shall be seen there is considerable controversy over this issue (see section 4.1.4 and later discussion).

2.2 Left ventricular hypertrophy also predicts cardiovascular risk in populations of African descent

Are there ethnic-specific effects of LVH as a predictor of CVD? The BP-independent predictive power of LVH as a risk factor for CVD as described in Caucasian populations is not specific for this ethnic group. Indeed, a number of studies conducted in groups of African ancestry support a similar conclusion. In a cross-sectional study in hypertensive African-American males, LVH was associated with the severity of coronary disease independent of conventional BP (Robinson et al 1993). Moreover, among an African-American cohort, independent of conventional BP, LVH was associated with a greater relative risk of coronary multivessel disease, LV dysfunction and an adverse survival rate (Liao et al 1995). In a bi-racial population (20% were African Americans)-based study with mean follow-up of 6.5 years, LVH conferred a 2-to-3 times higher adjusted hazard ratios for incident coronary heart disease and congestive heart failure (CHF) independent of hypertension status (Gardin et al 2001). In the Atherosclerosis Risk In Communities (ARIC) study, a prospective epidemiologic study conducted in an African-American population, LVH as detected by echocardiography and/or electrocardiography was a precursor of premature cardiovascular morbidity and mortality across all ethnic groups, even after adjusting for conventional risk factors including BP (Nunez et al 2005). Thus LVH appears to predict CVD in both groups of European and African ancestry. However, without exception these studies have been performed in population groups outside of Africa. Whether the same effects would be noted in groups of African descent living in developing communities in Africa has never been assessed.

2.3 Regression of left ventricular hypertrophy reduces cardiovascular risk

Clearly if LVH predicts the risk of future CVD, then regression of LVH should predict a reduced risk of CVD. One method of reducing LVM and decreasing the prevalence of LVH and concentric remodeling is through antihypertensive treatment (Wachtell et al 2002). It is now well recognized that regression of LVH with antihypertensive therapy is associated with reduced risk of CV morbidity and a decrease in coronary heart disease (CHD) and CV death rates (Heyden Hypertension Detection and Follow-up Program Cooperative Group, 1985, Levy et al 1994). Importantly however, there is now evidence to indicate that the impact of therapeutic agents on either ECG-determined LVH or echocardiographically-determined LVM and the associated CVD risk reduction is partly independent of office BP changes (Mathew et al 2001; Okin et al 2004; Devereux et al 2004[2]). These studies have therefore produced further provocative evidence to indicate that the relationship between LVM and associated CVD risk in hypertension may not be as tightly linked to BP changes as would normally have been predicted. In other words, LVM appears to predict a CV change that cannot simply be attributed to BP as measured using conventional techniques alone. Nevertheless, as will be discussed in subsequent sections, this conventional BP-independent effect may still be related to BP, but simply not that well predicted by conventional BP measurements. In other words, measures or indices that inform us of BP over prolonged periods, or in areas of large vessels closer to the heart than the brachial artery, may be better predictors of LVM.

2.4 Why is left ventricular hypertrophy associated with worse clinical outcomes independent of blood pressure?

Assuming that the relationship between LVM and CV outcomes is not simply because LVM is an index of the sum of all BP changes over time, then how could LVM

increase CVD risk? As LVH decreases LV wall stress, but yet is still associated with adverse CV outcomes, it is important to consider the potential reasons for these worse outcomes. The potential cardiac changes that may influence cardiac-related CV outcomes have been summarized by Messerli (1996). Left ventricular hypertrophy could lead to an impaired filling of the LV through both a decreased early-diastolic relaxation and a reduced late-diastolic compliance, changes that result in diastolic dysfunction. This, in-turn, may increase cardiac filling pressures, augment myocardial transmural pressures during diastole and reduce coronary flow (reduced coronary reserve) (Lorell et al 1987). Left ventricular hypertrophy could also result in an impaired LV pump function through a number of mechanisms including chamber dilatation (Norton et al 2002) and a decreased myocardial contractility (Malik et al 1974). Further, the increased tissue bulk of the myocardium may increase myocardial oxygen demand (Kannel et al 1970, Ghali et al 1991) an effect that may not be accompanied by the expected increase in coronary flow because of reductions in coronary reserve. Alterations in myocardial oxygen demand-to-supply ratios could result in programmed cell death (apoptosis) (Liu et al 2000) and necrosis (Tsotetsi et al 2001). Further, LVM is associated with neurohormonal activation and excessive myocardial sympathetic effects (Drazner et al 2004, Schlaich et al 2003), which could promote the transition to heart failure (Badenhorst et al 2003; Veliotes et al 2005).

Although there are many potential mechanisms that may explain the impact of LVH on myocardial pathology, the relationship between LVH or its regression and strokes (Di Tullio et al 2003, Okin et al 2004; Devereux et al 2004[2]) is more difficult to understand. It is possible that increased filling pressures in the LV and hence in the left atrium may result in atrial fibrillation and mural thrombus formation, an effect that could result in an embolic phenomenon. However, many strokes in patients with LVH are not from emboli from the heart. It is possible that LVH may predict early endothelial dysfunction and structural changes in large and small vessels (Muiesan et al 2004). Indeed, there is an association between vascular damage in small resistance arteries

and concentric hypertrophy (Palatini et al 1998, Wachtell et al 2000, Treasure et al 1993, Muiesan et al 2002). These changes in the brain or extracranial vessels, which would occur in conjunction with LVH, could lead to strokes.

3.0 Ethnic disparities in left ventricular mass and geometry

Whilst data from some early studies have suggested that after adjusting for BP, ethnicity is not associated with an increased prevalence of LVH (Hammond et al 1984, Gottdiener et al 1994) other early studies indicated that LVM index is increased in African-Americans as compared to Caucasians after BP adjustments (Dunn et al 1983) and that concentric LVH occurs more frequently in elderly African Americans with hypertension as compared to Caucasians (60% as compared to 39%) (Savage et al 1987). However, as will be discussed, uncertainties raised by these relatively inconsistent findings in earlier studies have nevertheless been resolved in more recent studies and in studies with large or relatively larger study samples.

It is now well documented that LVH is more prevalent amongst subjects of African ancestry than in Caucasian subjects (Koren et al 1993, Gardin et al 1995, Zabalgoitia et al 1998, Skelton et al 2003, Lorber et al 2003, Kizer et al 2004, Rodriguez et al 2004, Drazner et al 2005). Of particular relevance, in the Dallas Heart Study, conducted in over 2000 individuals, where more accurate methods of assessment of LVM were utilized (magnetic resonance imaging) than the usual method of echocardiography, African-Americans had an increased LVM even after adjustments for other determinants of LVM, including fat mass, fat-free mass, systolic BP, age, gender and measures of socioeconomic status (Drazner et al 2005). These findings are in agreement with the Hypertension Genetic Epidemiology Network Study, where over 1000 African-Americans had a greater LVM and LV relative wall thickness than 580 Caucasians after adjustment for confounding variables (Kizer et al 2004). In a study comparing African-American to European-American youth, ethnicity effects on LVM

appeared in early adolescence, and persisted even when controlling for anthropometric factors, haemodynamic variables and socioeconomic status (Dekkers et al 2002). Moreover, in a small study sample of African-Americans (n=82) and Caucasians (n=63), where ethnicity, gender, 24-hour BP, adiposity indices, plasma lipid concentrations, apo-lipoprotein concentrations and fasting insulin were included in the regression model, ethnicity was the most powerful predictor of LVM index (El -Gharbawy et al 2001). Studies performed on groups of African descent recently emigrated from Africa also support the notion that groups of African ancestry have a greater prevalence of concentric LVH (Abassade et al 1996[1]; Abassade et al 1996[2]).

With respect to the LV remodeling process associated with LVH, in previously untreated patients with essential hypertension relative wall thickness was noted to be greater in African-American subjects as compared to Caucasians (Mayet 1994). More recent studies clearly support this view. Indeed, a 6-fold higher prevalence of concentric remodeling has been reported in African-Americans as compared to Caucasians (Olutade et al 1998).

Despite the overwhelming evidence to indicate that LVM is greater in groups of African as compared to European ancestry, whether this effect is because of biological differences or because of differences in environmental factors has not been established. The impact of ethnicity on LVM appears to be stronger in subjects with higher BP values (Drazner et al 2005), suggesting that BP may still be the major factor influencing the impact of ethnicity on LVM. However, there are no studies that have been conducted in groups of African descent living in Africa that have attempted to determine whether LVM is characteristically higher in these groups as well. A higher LVM in subjects of African origins living in Africa would support a biological difference. This prompted me to define thresholds (partition values) for LVM in clinically normal individuals from randomly selected families in an urban developing community of African descent in South Africa. These data and the implications thereof are discussed in chapter 2 of this thesis.

4.0 Determinants of left ventricular hypertrophy

Many would still argue that the disparities between ethnic groups with respect to LVM and remodeling could be accounted for by co-morbidities or factors that may or may not be considered in epidemiological studies. Consequently, it is worth discussing some of the major determinants of LVM and the potential factors that could cause LVH.

Together with normal growth-related changes, there are several consistent factors that influence the development of LVH such as systemic BP, adiposity and body size, age and male gender. Left ventricular hypertrophy has also been associated with physical activity, genetic factors and arterial stiffness (Post et al 1994). The following outlines the evidence to support a role for some of these factors and the potential ethnic differences that may exist.

4.1 Blood Pressure

As indicated in earlier sections of this chapter, if BP in systemic arteries and hence the LV increases, the LV wall hypertrophies. An increase in systemic BP (hypertension) is a major cause of increases in LV pressures during the ejection phase of the cardiac cycle. Thus, not surprisingly, systemic hypertension is a primary determinant of LVH. However, some time ago it was recognized that the correlation between conventional BP and LVM is not as consistent as one would expect (Devereux et al 1987). This relationship may be so poor as to be undetectable in some groups. Indeed, in previous studies conducted in Caucasian hypertensives and normotensives (Bauwens et al 1991, Cerasola et al 1991, Polonia et al 1992) and in a recent study conducted in Congolese hypertensive patients of African ancestry (Lepira et al 2006), the relationship between conventional BP and LVM or LVH was almost absent or indeed was absent. A potential explanation for these unusual findings is that the haemodynamic load on the LV cannot be predicted from office or clinic (conventional) BP

measurements, measurements obtained at a single point in time (Devereux et al 1987). Indeed, early studies conducted at this time showed that LVH correlated better with BP measured during normal activity than at rest (Devereux et al 1987) and that the best correlation with LVM in Caucasians was with daytime BP (Frohlich et al 1992).

Based on the premise that BP measured during activity may be a better predictor of LVM than resting BP values, a number of studies have been conducted to test the hypothesis that ambulatory BP is a better predictor of LVM than conventional BP. Moreover, these studies explored whether daytime or night-time BP values are better predictors of LVM and whether the nocturnal decline in BP contributes toward the variability in LVM. These studies will be described in the following sections.

4.1.1 Ambulatory or conventional BP: Which is better correlated with left ventricular mass in cross-sectional studies?

Many cross-sectional studies with small or relatively small sample sizes have reported on the superiority of ambulatory BP over conventional BP when predicting LVM (reviewed by Fagard et al 1995[1]). The majority of these studies were conducted in study samples which ranged from small to reasonably large (n=12-to-235). An analysis of the relationship between the correlation coefficients of the office BP-LVM and ambulatory BP-LVM relations of many of these studies has been particularly revealing (Fagard et al 1995[1]). This analysis supported a conclusion that some clinic BPs may predict LVM as well as ambulatory BP, rather than a conclusion that ambulatory BP is indeed superior to clinic BP in predicting LVM (Fagard et al 1995[1]). In this regard, multiple visits may be required to obtain a better assessment of the relationship between conventional BP and LVM (Prisant and Carr 1990). Moreover, the assessment of conventional BP in a quiet room may produce just as close a correlation with LVM as ambulatory BP (Ganau et al 1990). The use of the same observer and multiple conventional BP measurements (5 at each visit) at two visits in a quiet room at a similar time of day was also associated with

similar correlation coefficients between conventional and ambulatory BP and LVM (Fagard et al 1992). Thus, there is still no real consensus as to whether ambulatory BP is superior to conventional BP in predicting LVM in cross-sectional studies. This is a particularly important question in developing communities where access to ambulatory BP monitoring in minimal resource settings is almost non-existent. Hence, as part of my thesis, I studied in a relatively large community-based sample, whether ambulatory BP is superior to conventional BP. These data and the implications thereof are reported on in chapter 3 of this thesis.

4.1.2 Diurnal variations in BP and the impact on left ventricular mass

It is still not clear which component of the 24-hour BP profile best predicts LVM or CVD. An attenuated nocturnal decrease in BP or nocturnal rather than daytime BP *per se* has been associated with lacunar infarcts (Yamamoto et al 1998), cardiovascular outcomes in the elderly with isolated systolic hypertension (Staessen et al 1999), in hypertensives in general (Verdecchia et al 1994, Zweiker et al 1994), in the general population (Ohkubo et al 1997, Kikuya et al 2005) and in type II diabetes mellitus (Nakano et al 1998) independent of conventional BP values. Some studies have suggested that night-time, but not daytime systolic BP predicts LVM in normotensives and hypertensives (Mayet et al 1998, Verdecchia et al 1994, Morfis et al 2002). Moreover, other reports have indicated that an attenuated nocturnal fall in BP or "non-dipping" is associated with LVH (Verdecchia et al 1990, Verdecchia et al 1992, Schmieder et al 1995). However, there is also considerable controversy in this regard as others have demonstrated no relationship between nocturnal decreases in BP and LVM (Schulte et al 1993, Boley et al 1997, Roman et al 1997). Moreover, a meta-analysis revealed that daytime BP is an equivalent predictor of LVM as compared to night-time BP, and that the differences between day and night-time BP explain only 15% of LVM index (Fagard et al 1995[2]). Moreover, more recent studies have also indicated that

daytime BP is an equivalent predictor of both echocardiographic and electrocardiograph indices of LVM as compared to night-time BP in untreated hypertensive patients (Feola et al 1998; Cicconetti et al 2003, de la Sierra et al 2002). However, what has not been appropriately addressed is whether daytime, night-time or day-night differences in BP are of particular relevance as predictors of LVM in groups of African descent. Importantly, all of the large or relatively studies assessing the relative impact of day, night or day-night differences in BP on LVM have been conducted in groups largely of European descent. However, as compared to groups of European ancestry it is groups of African ancestry who have attenuated nocturnal decreases in BP (Profant and Dimsdale 1999; Wang et al 2006). It is therefore possible that disparities in LVM between ethnic groups may be accounted for by an impact of diurnal variations in ambulatory BP. Indeed, conventional BP assessment may underestimate the severity and duration of a high BP especially amongst subjects of a lower social economic status (Rodriguez et al 2004). It is well recognized that groups of African descent, through ethnic discrimination, generally have a lower mean socioeconomic status.

In contrast to the number of studies assessing the impact of day, night or day-night differences in BP on LVM in groups of European descent, few such studies have been conducted in groups of African descent. Some studies suggest that nocturnal rather than daytime systolic BP influences LVM in groups of African descent (El-Gharbawy et al 2001, Mayet et al 1998, Hinderliter et al 2004). However, these studies were generally performed in small sample sizes (n=46-to-88) (El-Gharbawy et al 2001, Mayet et al 1998, Hinderliter et al 2004). Moreover, other large studies (n=426 subjects of African descent) have suggested that daytime rather than nocturnal BP is associated with LVM in groups of African descent (Chaturvedi et al 1994). Nevertheless, in this study (Chaturvedi et al 1994), the investigators only used two hours of BP measurements to describe each of daytime and nocturnal BP. No study with a large sample size conducted in groups of African descent and with appropriate ambulatory BP values has specifically reported on relationships between day-night differences in BP

and LVM. Consequently, as part of the present thesis I also studied the relative impact of day, night and day-night differences in ambulatory BP on LVM in a large community-based sample of a group of African descent. These data and the implications thereof are described in chapter 3 of the present thesis.

4.1.3 Ambulatory or conventional BP: Which is better correlated with the regression of left ventricular hypertrophy in groups of European descent?

With respect to the relative impact of conventional or ambulatory BP on the regression of LVH, some studies conducted in Caucasians indicate that ambulatory BP is either superior to conventional BP in predicting treatment-induced changes in LVM or adds to the value of predicting treatment-induced changes in LVM (Koren et al 1991, Fagard et al 1997[3], Mancia et al 1997, Redon et al 1998, Mancia et al 2003). Moreover, in a recent meta-analysis that compared office BP to ambulatory BP in assessing the response of LVM to antihypertensive treatment, ambulatory BP was superior to office BP (Mancia et al 2004). However, controversy exists as to which BP measurement (conventional or ambulatory) best predicts changes in LVM with antihypertensive treatment (Fagard et al 1997[3]). In this regard, large studies are multicentric, which makes the standardization of conventional BP measurements more difficult to achieve.

In contrast to data that indicate that ambulatory BP is a better predictor of changes in LVM with treatment, in the Pressione Arteriose Monitorate E Loro Associazioni (PAMELA) study, if patients achieved BP control, LVM index was markedly decreased regardless of whether the BP was assessed by office, home or ambulatory measurements (Mancia et al 2002). Moreover, in the PAMELA study, ambulatory and conventional BP predicted CVD equally as well (Sega et al 2005). Nevertheless, the PAMELA study also demonstrated that the addition of nocturnal BP to the regression model which included conventional BP improved the strength of the relationship with CV events (Sega et al 2005).

As indicated in the above discussion (section 4.1.2), as compared to groups of European ancestry, groups of African ancestry have attenuated nocturnal decreases in BP (Profant and Dimsdale 1999, Wang et al 2006). It is therefore possible that decreases in nocturnal BP may translate into a closer relationship between changes in ambulatory BP and LVM, than between changes in conventional BP and LVM in groups of African ancestry receiving antihypertensive treatment. Prior to the studies reported on in this thesis there were no prospective studies assessing whether ambulatory BP is a better predictor of on-treatment LVM than conventional BP in groups of African descent. These studies were conducted as part of my thesis and the outcomes reported on in chapters 5 and 6.

4.1.4 Diurnal variations in BP: Impact on the regression of left ventricular hypertrophy

With respect to day versus night BP effects on the regression of LVH in groups of European ancestry, in the Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation (SAMPLE), daytime and night-time BP were equally important in predicting the reduction in LVM (Mancia et al 1997). These data are also supported by a smaller study demonstrating a similar impact of day and night BP on treatment induced changes in LVM (Fagard et al 1997[3]). Moreover, day-night differences in BP were not associated with on-treatment changes in LVM (Mancia et al 1997, Fagard et al 1997[3]). However, this does not preclude a potentially important role for diurnal variations in BP as contributing toward changes in LVM over time. Indeed, antihypertensive treatment decreases rather than increases day-night differences in BP (Fagard et al 1997[3]). Moreover, it is difficult to control for absolute BP changes over time when assessing the relationship between day-night differences in BP and LVM. Hence, longitudinal studies designed to resolve the role of diurnal variations in BP as determinants of LVM are difficult to conduct. Nevertheless, as part of the present thesis, although I did not aim to assess the importance of day-night

differences in BP on treatment-induced changes in LV mass, I did evaluate the relative impact of sequential day and night BP values on LVM in hypertensives on treatment. This is particularly important considering that some small studies have suggested that nocturnal rather than daytime systolic BP influences LVM in groups of African descent (El-Gharbawy et al 2001, Mayet et al 1998, Hinderliter et al 2004) and as indicated in the above discussion, that groups of African descent have an attenuated nocturnal decline in BP (Profant and Dimsdale 1999, Wang et al 2006).

4.2 Body size

Body size is the most consistent determinant of LVM. The strong relationship between body size and LVM is supported by a number of studies with large sample sizes (Lauer et al 1991, Lauer et al 1992, de Simone et al 1992, Gottdiener et al 1994, Urbina et al 1995, Gardin et al 1995, Sherif et al 2000; Lorber et al 2003; Fox et al 2004). Importantly, in large cohorts of mild-to-moderate hypertensive patients, body mass index (BMI) is the strongest predictor of LVM (Lauer et al 1992, Gottdiener et al 1994). The effects of body size may be through either the impact of adiposity and muscularity, effects which are accounted for by indexing LVM for body surface area, or simply by growth effects, which are in-turn, accounted for by indexing LVM for height. The effects of adiposity are thought to be through the effects of fat-free mass (Drazner et al 2005). However, the relationship between body size and LVM may not be restricted to lean body mass only. Indeed, in healthy young Caucasian and African-American adults of the Coronary Artery Risk Development in Young Adults (CARDIA) cohort study, a strong correlation was found between LVM and subscapular skin-fold thickness in both genders and ethnic groups (Gardin et al 1995). Similarly, in pre-menopausal American women LVM index correlated with indexes of central adiposity (Sherif et al 2000).

Importantly, when indexing LVM for height to account for growth but not adiposity effects, the relationship between height and LVM is an exponential function (de Simone

et al 1992, de Simone et al 1995). Hence a power function is used to adjust for the exponential relationship with the power function generally used being height$^{2.7}$ (de Simone et al 1992, de Simone et al 1995). Based on CV outcomes, normal values for LVM indexed for allometric height signals have been described in populations of European ancestry and African descent originating from West Africa (Nunez et al 2005). Both of these population groups are nevertheless taller than those noted in groups of African descent living in South Africa (see chapter 2). Whether the relationship between LVM and height in shorter populations fits the same exponential function as that in taller groups has not been established. One study conducted in groups of African descent with a shorter stature has indicated that adjustment for height to the first power rather than to the power of 2.7 eliminates LVM/height-height relations (Jaggy et al 2000). Indexing for height$^{2.7}$, may therefore underestimate LVM thresholds in groups of African descent with a shorter stature. Consequently, in the present thesis I evaluated the relationship between LVM and allometric (growth) signals in a community of African descent living in Africa with mean values for height lower than those described for other populations. This study was conducted in order that thresholds for LVM index could be defined for healthy adults of African descent living in South Africa using an appropriate index, and these thresholds could then be compared against thresholds defined for other population groups. These data and the implications thereof are described in chapter 2 of the present thesis.

4.3 Arterial stiffness and its relationship with cardiovascular disease and left ventricular mass

It is now well recognized that changes in the characteristics of the wall of large arteries (wall thickness and compliance) are predisposing factors for CVD (Blacher et al 1999, Black et al 1999, de Simone et al 1999, Laurent et al 2001, Boutouyrie et al 2002, London et al 2001, Safar et al 2002, Guerin et al 2001, Saba et al 1993; Blacher et al 2005; Chaturvedi et al 2004, Dolan et al 2006). Indices of aortic stiffness are independent predictors of CV events in patients with hypertension (de Simone et al 1999, Laurent et al 2001, Boutouyrie et al 2002), in patients referred to tertiary care centres (Dolan et al 2006) and in patients with end stage renal disease (London et al 2001, Safar et al 2002, Guerin et al 2001, Nitta et al 2004). These effects are independent of conventional or ambulatory (Dolan et al 2006) BP measurements. Moreover, indices of arterial stiffness are associated with pump dysfunction in chronic heart failure (Tartiere et al 2006), with a concentric LV geometry in hypertension (Palmieri et al 2003) and with LV diastolic dysfunction in hypertension (Palmieri et al 2003), effects that are also independent of conventional BP.

Arterial stiffness contributes toward CVD, in-part through the impact of early reflective waves on central aortic pressures, a pressure that is not accurately predicted by brachial artery BP measurements (Karamanoglu et al 1993, Williams et al 2006). The effects on the heart could be through an increased LV afterload and a decreased coronary perfusion subsequent to the development of LVH (see section 2.4 above). However, although preclinical studies provide evidence to suggest that central rather than peripheral BP predicts LV remodelling (Kobayashi et al 1996), as shall be discussed, whether a conventional BP-independent relationship between arterial stiffness and LVM exists is unclear.

Although many studies have shown that indices of arterial stiffness are associated with LVM (Tatchum et al 1995, Kobayashi et al 1996, Bouthier et al 1985,

Boutouyrie et al 1995, Roman et al 1996, Chen et al 1998, Roman et al 2000, Baguet et al 2000, Iketani et al 2000, Deague et al 2001, Gates et al 2003, Leoncini et al 2006) in this regard, much of the evidence indicates that measures of arterial stiffness do not provide information beyond that afforded by measures of brachial artery (peripheral) systolic BP. Only two human studies suggest that arterial stiffness effects on LVM are independent of brachial artery BP (Lekakis et al 2004, Leoncini et al 2006), one of which was conducted in a very small study sample (Lekakis et al 2004), and another was a study relating the less well recognized ambulatory arterial stiffness index with LVM (Leoncini et al 2006). In contrast, a number of papers have indicated that the relationship between indices of arterial stiffness and LVM is dependent on conventional BP measured at the brachial artery (Bouthier et al 1985, Roman et al 1996, Chen et al 1998, Roman et al 2000, Baguet et al 2000, Deague et al 2001). Nevertheless, clinical studies assessing the relationship between arterial stiffness and LVM have largely been conducted in groups of European descent (Bouthier et al 1985, Boutouyrie et al 1995, Roman et al 1996, Chen et al 1998, Roman et al 2000, Baguet et al 2000, Iketani et al 2000, Gates et al 2003, Deague et al, 2001, Lekakis et al 2004, Leoncini et al 2006). However, arterial stiffness appears to be higher in people of African ancestry as compared to Caucasians (Din-Dzietham et al 2004; Shiburi et al 2006; Chaturvedi et al 2004). The question therefore arises as to whether the impact of arterial stiffness on LVM in groups of African descent is in-part independent of BP measured at the brachial artery. If this is so, this may partly explain the increased LVM noted in groups of African ancestry. Therefore as part of the present thesis I also aimed to assess whether indices of arterial stiffness are associated with LVM and geometry independent of conventional BP in a relatively large, randomly selected population sample of African descent. These data are presented in chapter 4 of this thesis.

5.0 Class-specific effects of therapeutic agents on the regression of left ventricular hypertrophy

As indicated in section 2.4 above, there is evidence to indicate that the impact of therapeutic agents on LVM and the associated CV risk reduction is partly independent of conventional BP changes (Mathew et al 2001; Okin et al 2004; Devereux et al 2004[2]). The notion that specific antihypertensive classes of agents may have unique beneficial properties on target organ effects originally arose from animal studies demonstrating that non-specific vasodilators, such as minoxidil and hydralazine have little effect on LVM in animal models of hypertension, despite producing profound antihypertensive effects (e.g. Tsotetsi et al 2001). This notion was further extended in a number of human studies that were subsequently formally reviewed in a series of systematic reviews and meta-analyses of these smaller studies. In this regard, two meta-analyses, which included uncontrolled studies in the analysis, revealed therapeutic class-specific effects. In a meta-analysis by Dahlof including 109 treatment studies, angiotensin-converting enzyme inhibitors (ACE-Is) and calcium channel blockers (CCBs) were noted to produce a more pronounced reduction of LVH than other drug classes (Dahlof et al 1992). Moreover, in a meta-analysis conducted by Schmieder et al (1998) with 89 randomized double-blind studies included in the analysis, ACE-Is and CCBs were noted to produce a greater decrease in LVH than beta-blockers or diuretics. In contrast however, a meta-analysis conducted by Fagard[3] (1995) which included 21 controlled treatment studies, the reduction of LVM produced by antihypertensive agents was similar across the drug classes studied including diuretics, CCBs, beta-blockers and/or ACE-Is (Fagard 1995[3]).

Based on the notion that some classes of antihypertensive agents may be superior to others in their ability to reduce LVM in hypertension, further large studies were conducted with direct comparisons made between specific classes of agents. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, the angiotensin II receptor blocker, losartan, produced a greater regression of LVM than did

a beta-adrenergic receptor blocker, atenolol, after adjusting for conventional BP effects (Devereux et al 2004[1]). This class-specific effect of losartan was mainly mediated by a decrease in LV septal and posterior wall thickness, rather than through changes in internal dimensions (Devereux et al 2004[1]). The specific conventional BP-independent benefits of losartan on LVM in the LIFE study were also associated with a class-specific effect on CV risk reduction. As compared to the beta-blocker treated group, the overall greater CV risk reduction in hypertensive patients with LVH, treated with losartan, was 13% (Dahlof et al 2002[1]). The risk reduction was achieved for the composite end-point of CV death, stroke and MI, and especially for fatal and non fatal stroke (Dahlof et al 2002[1]). The data from the LIFE study are further supported by a study conducted with a similar design, where the angiotensin II receptor blocker, losartan, was also found to be superior to the beta-blocker atenolol at regressing LVH despite comparable effects on conventional BP (Zanchetti et al 2002).

Although there is now substantial evidence to indicate that agents that block the renin-angiotensin system (RAS), such as angiotensin II receptor blockers, may reduce LVM in hypertensives to a greater degree than beta-adrenergic receptor blockers independent of conventional BP measurements, RAS blockers may still produce equivalent effects as compared to other antihypertensive agents such as CCBs. Indeed, in the Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement (PRESERVE) Trial, ACE-Is and CCBs (with the addition of diuretics) produced similar effects on LVM in patients with hypertension and LVH (Devereux et al 2001).

5.1 Potential mechanisms of class-specific effects of therapeutic agents on the regression of left ventricular hypertrophy

There are several explanations why blockers of the RAS may have a superior effect on the regression of LVH, whilst beta-blockers may not perform as well after

adjusting for conventional BP values. Blockers of the RAS may reduce the accumulation of collagen in large vessels and subsequently increase arterial compliance to a greater extent than other antihypertensive agents (Safar et al 1986). As indicated in section 4.3 above, the effect of changes in arterial compliance on central BP may not be detected at the brachial artery (Karamanoglu et al 1993, Williams et al 2006). Although this issue is controversial (Weinberg et al 1997), blockers of the RAS may also reduce the effect of angiotensin II on the growth of cardiac myocytes independent of BP effects (Weinberg et al 1997).Therefore blocking angiotensin II production may favor the regression of LVH irrespective of BP effects (Ji et al 2003; Cagalinec et al 2006). However, the conventional-BP independent effect of RAS blockers on LVM may still be through BP effects. Indeed, blockers of the RAS may also produce a greater reduction in 24-hour BP than other classes of agents (Dahlof et al 1992). Clearly adjusting for conventional BP as opposed to ambulatory BP when assessing class-specific effects on LVM, is likely to have no impact if therapeutic agents have different ambulatory but the same conventional BP effects.

As will be argued, the class-specific effect of RAS blockers on the regression of LVH in groups of African descent is in-question. Hence, as part of the present thesis I studied whether on-treatment LVM index is more closely related to the use of an ACE-I or to BP in South Africans of African ancestry with mild-to-moderate hypertension over a two-year treatment period. This study is described in chapter 6 of the present thesis. As it is possible that RAS blocker-specific effects on LVM may be through a greater reduction in 24-hour BP than other classes of agents (Dahlof et al 1992) in this study I employed ambulatory BP monitoring to assess BP effects on LVM.

5.2 Ethnic differences in class effects of therapeutic agents on the regression of left ventricular hypertrophy and cardiovascular outcomes

In contrast to data obtained from meta-analyses in Caucasian groups (Dahlof et al 1992, Schmieder et al 1998), ACE-Is and diuretics appear to produce a similar reduction in LVM in South Africans of African ancestry (Middlemost et al 1994). In addition, when used as monotherapy, CCBs are superior to the ACEI, enalapril, in reducing LVM in severe and in mild-to-moderate hypertensive patients of African descent (Radevski et al 1999; Skoularigis et al 1994). Moreover, in the Baragwanath Hypertension Study, a relatively large single-centre study conducted in South African hypertensives of African ancestry, we were able to show that the decrease in LVM index produced by CCB, diuretic and ACE-I treatment groups did not differ between these different therapeutic classes over four months of therapy (Sareli et al 2001). Thus in South Africans of African descent at least, there is evidence to indicate that agents that block the RAS have no greater benefits over other antihypertensives when assessing their effects on LVM. However, this still requires clarity as maximal regression of LVH with antihypertensive agents may take up to two years to achieve (Devereux et al 2002).

The inability of agents that block the RAS to produce a greater degree of regression of LVM as compared to other agents in black South Africans is reflected by data obtained in African-Americans. Indeed, in the LIFE study, a greater propensity of the angiotensin II receptor blocker, losartan to decrease LVM as compared to atenolol was noted in Caucasians, but not in other ethnic groups. Indeed, in a small cohort of other ethnic groups a significant decrease in LVM was not achieved with losartan (Devereux et al 2004[1]). The lack of ability of losartan to decrease LVM to a greater extent than atenolol in the LIFE study was also mirrored by an inability of losartan to produce greater effects on CV outcomes as compared to atenolol in African-Americans patients (Julius et al 2004). Indeed the overall analysis on CV outcomes favored atenolol as opposed to losartan (Julius et al 2004). The ethnic-specific effects of agents that block

the RAS on CV outcomes were also noted in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). In the ALLHAT study, in which 35% of the patients enrolled were African-Americans, a significant interaction between ethnic group and treatment was noted when comparing the ACE-I, lisinopril, to the diuretic treatment group with respect to stroke and CVD (Julius et al 2004).

The lack of consensus as to whether RAS blockers produce effects on LVM independent of BP changes in groups of African descent prompted my colleagues and I, as part of my thesis to extend the Baragwanath Hypertension Study from four months to two years. In this study I evaluate whether the use of an ACE-I confers benefits on changes in LVM beyond that produced by BP effects. This study and the implications thereof are described in chapter 6.

5.3 Potential explanations for the impact of ethnicity on class effects of antihypertensive agents on left ventricular mass and other target organs

A number of factors could explain the distinct ethnic differences in the RAS class effects of antihypertensive agents on LVM and other target organs. One potential explanation is that the BP response of hypertensives of African descent may differ for some treatment regimens (Cushman et al 2000, The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002). Indeed, in the ALLHAT study, the reduction in systolic BP (4 mmHg) in the lisinopril (ACE-I)-treatment group was lower in African–Americans as compared to Caucasians and other ethnic groups (The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002) a finding that has been widely incorporated into guidelines (Chobanian et al 2003, Williams et al 2004). These data are consistent with what is presently known to occur in South Africans of African descent. It is well recognized that ACE-Is, when used as monotherapy, have little antihypertensive effect in South Africans of African ancestry, an effect that appears to be genetically pre-determined (Woodiwiss et al 2006).

Importantly however, the class-specific effect of ACE-Is on LVM may still occur in South Africans of African ancestry. Indeed, a similar reduction in LVM in South Africans of African ancestry in response to ACE-Is as compared to diuretics may occur even without a BP effect (Middlemost et al 1994). Thus in South Africans of African ancestry at least, there is still question as to whether agents that block the RAS have a BP-independent effect on LVM regression, and if so whether this effect masks the BP-dependent effects of antihypertensive agents on LVM. If antihypertensive agents produce therapeutic benefits on LVM and hence presumably other target organs without a significant BP effect, then there is question as to whether BP can be used as a surrogate measure of target organ effects. This is an important question in groups of African ancestry, in whom electrocardiograph criteria are poor indicators of LVH (Lee et al 1992), thus necessitating the use of other clinical indicators of regression of LVH. With the present resource constraints in the public health sector, it is not possible to offer routine echocardiography during antihypertensive therapy. If neither echocardiograph nor electrocardiograph indices of LVH are either available or useful, the only surrogate of the regression of LVH is a measure of BP. If the regression of LVH with RAS blockers in patients of African descent is not closely associated with BP, then we are faced with the conundrum of having no clinical index which will inform us of target organ effects in groups of African descent. Consequently, as part of the present thesis I studied whether there is indeed a relationship between BP changes and changes in LVM following the administration of agents that block the RAS to black South Africans with hypertension. These data and the implications thereof are presented in chapter 7 of this thesis.

5.4 What is the best approach to the use of antihypertensive therapy in groups of African descent?

As indicated in the above discussion there is indeed an ethnic-specific effect of antihypertensive therapy in groups of African descent. These effects are for both BP

(Cushman et al 2000, The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002) and for LVM (Devereux et al 2004[1], Sareli et al 2001, Radevski et al 1999; Skoularigis et al 1994). How does this potentially impact on the management of hypertension in groups of African ancestry? The South African Hypertension Society and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) guidelines recommend thiazide diuretics as initial therapy for the treatment of uncomplicated hypertension (Hypertension Society of Southern Africa, [Seedat et al 2006], The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2003). As the major ethnic-specific effect of antihypertensive therapy appears to apply to ACE-Is and angiotensin II receptor blockers, and not to diuretics, this ethnic-specific effect of antihypertensive therapy may not impact on management decisions in groups of African descent.

However, there are many compelling indications for the use of RAS blockers in the treatment of hypertension, one of which is hypertension with LVH (Hypertension Society of Southern Africa, Seedat et al 2006, The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2003). As LVH is likely to be highly prevalent in groups of African descent (see section 3.0 above), the ethnic-specific effects of RAS blockers may pose a management decision problem. However, a potential solution to this dilemma is to start patients requiring RAS blockers on a diuretic and then to add a RAS blocker, a combination that is thought to be as efficacious as in other ethnic groups. However, low-dose thiazide diuretic agents do not achieve ambulatory BP control in patients of African descent (Skoularigis et al 1995). Moreover, in a multi-arm combination trial, a dihydropyridine calcium channel blocker (CCB) when used as monotherapy was shown to be more efficacious than other classes of antihypertensive agents including low dose hydrochlorothiazide (HCTZ) (12.5-25 mg daily), a thiazide diuretic, as determined from 24 hour ambulatory BP monitoring in patients of African ancestry (Sareli et al 2001). Thus, it appears at least from a BP

perspective, that efficacious first-line therapy in groups of African descent may not be diuretic agents, but rather CCBs.

Nevertheless, using ambulatory BP monitoring to assess efficacy, our group have recently demonstrated that monotherapy with the diuretic indapamide was superior to low dose HCTZ (Radevski et al 2002) in the management of hypertension in black African patients with mild-to-moderate hypertension. Whether indapamide used as initial therapy, with an ACE-I added as additional therapy, mediates equivalent antihypertensive actions and beneficial effects on LVM when compared to dihydropyridine CCB therapy in groups of African descent has not been evaluated. Therefore, as part of this thesis I compared the effect of indapamide plus an ACE-I to the dihydropyridine CCB, amlodipine on ambulatory BP and LVM in black patients with mild-to-moderate hypertension. This study and the implications thereof are described in chapter 8 of the present thesis.

6.0 Aims

The aims of the present thesis were therefore as follows:

a) To determine whether allometric growth signals (based on relationships between LVM and height) presently used to account for growth effects on LVM in taller populations are appropriate for a community of African descent living in Africa with a relatively short stature (chapter 2).

b) To assess threshold values for LVM in clinically normal individuals from a randomly selected cross-sectional sample of nuclear families in a community of African descent living in Africa and consequently to compare these thresholds with other population samples (chapter 2).

c) To determine whether ambulatory BP is more closely associated with LVM than conventional BP or associated with LVM independent of conventional BP in a randomly selected cross-sectional sample of nuclear families in an urban, developing community of African descent (chapter 3).

d) To determine the relative impact of day, night and day-night differences in BP on LVM in a randomly selected cross-sectional sample of nuclear families in an urban, developing community of African descent (chapter 3).

e) To determine whether indices of arterial stiffness are associated with LVM independent of conventional BP in a randomly selected cross-sectional sample of nuclear families in an urban, developing community of African descent (chapter 4).

g) To determine whether the regression of LVM in hypertensives of African origins is more closely associated with ambulatory than conventional BP over 4 months of antihypertensive treatment in newly diagnosed patients (chapter 5) and over 2 years in a combination of newly diagnosed and previously treated patients (chapter 6).

h) To determine whether the use of RAS blockers confers specific benefits over other agents in reducing LVM in hypertensives of African origins (chapter 6) and whether RAS blockers mask the BP-dependent effect of antihypertensives on the regression of LVM in hypertensives of African origins (chapter 7).

i) To determine whether a diuretic-ACEI combination is equally effective as a CCB in regressing LVM in hypertensives of African descent (chapter 8).

Chapter 2

Partition Values for Left Ventricular Mass in Subjects of African Descent in South Africa.

ABSTRACT

Left ventricular (LV) hypertrophy is an independent risk factor for CVD. Population thresholds for LV mass (LVM) have been almost exclusively defined in groups residing in non-African countries. Unlike other population samples where growth exponentially impacts on LVM, in Southern Africa LVM may be linearly related to growth. Thresholds for LVM indices in populations where LVM is linearly related to growth have not been determined. In healthy participants (n=141) of randomly selected nuclear families of African descent living in an urban, developing community in South Africa (Soweto)(n=399 participants older than 16 years) I determined the appropriate adjustments of LVM for body size and subsequently assessed the thresholds for LVM indexed to these growth signals. The relationship between height and LVM was markedly different from that reported on in other population groups. LVM was related to body weight to the first power ($r=0.42$, $p<0.001$), body surface area (BSA) to the first power ($r=0.46$, $p<0.001$) and height to the first power ($r=0.39$, $p<0.0001$). No residual relation of LVM/BSA to BSA ($r=0.04$, $p=0.61$) was noted, whereas an inverse relation between LVM/body weight and body weight and a positive relation between LVM/height and height was noted. Expressing LVM for growth signals determined in other population groups ($height^{2.7}$), overadjusted LVM, with a negative relationship noted between $height^{2.7}$ adjusted LVM and height ($r=-0.24$, $p=0.003$) and $BSA^{1.5}$ adjusted LVM and BSA ($r=-0.19$, $p=0.02$). Partition values for LVM adjusted for BSA to the first power were only marginally higher than in studies conducted in ethnic groups of non-African descent or ethnic groups of African descent living in other African countries. These data suggest that in South Africans of African descent, allometric signals used to adjust for growth in other population groups overadjust LVM. Moreover, in groups of African descent living in South Africa, thresholds for LVM appropriately indexed for growth are only marginally greater than in other population samples of non-African ancestry or of African ancestry living in Africa.

2.1 INTRODUCTION

The importance of LVM as a determinant of CVD is now well established (Casale et al 1986; Levy et al 1990; Koren et al 1991; Levy et al 1994; Verdecchia et al 1996; Ghali et al 1998; Devereux et al 2004[2]; Okin et al 2004). In this regard, a number of recent studies with large sample sizes conducted in groups living outside of Africa indicate that LVM and the prevalence of LVH is considerably greater in groups of African than of European descent, and that ethnicity is a strong risk factor for LVH independent of all other factors including conventional BP, fat mass and fat-free mass (Skelton et al 2003, Lorber et al 2003, Kizer et al 2004, Rodriguez et al 2004, Drazner et al 2005). These ethnic differences in LVM may translate into an increased prevalence of CVD.

Thresholds for LVM have been almost exclusively defined in groups residing outside of Africa. There is considerable uncertainty as to whether LVM is indeed increased in groups of African descent in Africa. Difficulty in assessing whether LVM is increased in groups of African descent living in Africa occurs because growth relations with LVM may differ in these population groups. Unlike most population samples, where residual correlations between LVM and height are eliminated with the use of power functions ($height^{2.0 \text{ or } 2.7}$)(Lauer et al 1994, de Simone et al 1992, 1995), in groups of African descent living in Africa, where a shorter stature may occur, LVM indexed for height to the first power has been reported to eliminate residual correlations between LVM and height (Jaggy et al 2000). Unlike African-American groups that have been reported to have prevalence rates of LVH when adjusting LVM for $height^{2.7}$ of ~36-49% (Nunez et al 2005), groups of African descent living in Africa have LVH prevalence rates based on LVM indexed for height, of ~9% (Jaggy et al 2000). It is therefore possible that unlike in African-Americans, groups of African descent living in Africa do not have an increased LVM. In the present study I therefore aimed to identify the most appropriate relationships between growth and LVM in subjects of African ancestry living in an urban, developing community in South Africa, to subsequently identify thresholds for LVM

indexed for appropriate growth signals in healthy individuals in this community, and to compare thresholds for LVM indices obtained in healthy individuals against other population samples.

2.2 METHODS

2.2.1 Study group.

The study protocol was approved by the University of the Witwatersrand Committee for Research in Human Subjects (approval number: M02-04-72). To ensure quality control of the present study, investigators were trained at the University of Leuven in Belgium. In the present study, subjects of African ancestry were recruited from the township of Soweto (a metropolitan area of Johannesburg). Random recruitment of spouses and siblings living in households from formal dwellings (Figure 2.1) represented in the last census conducted (2001) was performed. Households were allocated numbers and numbers were selected from a random number generator. People residing in informal dwellings or institutions/homes were not recruited. The minimum age for participation in the study was 16 years, but there was no upper age limit. A lower age limit was included to avoid the impact of rapid growth effects.

Recruitment for the present study was initiated in October 2003 and data obtained up until November 2006 were used for the present thesis. The study design has been described in brief in a recent publication (Shiburi et al 2006). Substantially more participants have been recruited subsequent to this original analysis (Shiburi et al 2006). Of the 1058 subjects that were invited to be part of the study, 656 subjects (62%) agreed to participate. Of the 656 participants enrolled in the study, 418 (64%) agreed to echocardiograph assessments. I discarded 15 because echocardiograms were of poor

Figure 2.1. Examples of formal dwellings in the suburban region where people were recruited for this study.

quality and a further 8 who did not have conventional BP measurements obtained on three separate occasions as part of this study. Thus, in total 399 subjects were assessed in this study.

The subjects recruited were from the Nguni (Zulu, Xhosa, Ndebele, Swati), Sotho (South Sotho, North Sotho and Tswana) and Venda chiefdoms. The groups largely consisted of Nguni and Sotho chiefdoms. The lack of representation from the Venda chiefdom reflects a lack of individuals of this chiefdom residing in these areas of Johannesburg. No subjects of mixed, Asian, or European ancestry were recruited and no Khoi-San subjects were recruited. All subjects gave written, informed consent to participate in the study.

2.2.2 Questionnaire

Subjects completed a standard questionnaire. In order to avoid translational errors, the questionnaire was not translated into an African language, but study assistants familiar with all languages spoken in these townships and whom have either previously lived in Soweto or currently reside in Soweto, assisted with the completion of each questionnaire. Only same-sex assistants were used to assist each family member with the completion of the questionnaire. Assistance was only provided when requested. The majority of subjects were reasonably proficient in English. Study assistants first visited homes of subjects that agreed to participate in the study in order to develop a trusting relationship. The questionnaire was only completed at a subsequent clinic visit and then ambiguities checked by performing a follow-up home visit. If family members were absent at follow-up home visits, data was checked with them personally via telephonic conversations whenever possible. Ambiguities in answers to the questionnaire were detected by an independent observer prior to the second home visit. A pilot study was conducted in 20 subjects to ensure that data obtained in the

questionnaires were reproducible when obtained with the assistance of two separate study assistants.

The questionnaire requested specific answers to date of birth, gender, previous medical history, the presence of hypertension, diabetes mellitus and kidney disease, prior and current drug therapy (analgesic use included), prior and current occupation, level of education, smoking status (including the number of cigarettes smoked in the past and at the present time), daily alcohol consumption (beer, traditional beer or other forms of alcohol and the daily quantity), caffeine consumption (number of cups of tea or coffee and whether they are decaffeinated and the number of cola's a day), exercise frequency and family history of hypertension and cardiovascular events. For females, menstrual history, history of pregnancies and oral contraceptive use was evaluated. Although many of the questions simply required a "yes"-"no" answer, understanding was assessed by requesting some short answers. Although daily distances walked were requested, it was noted that perceptions of distance were largely overestimated and hence these data were not analysed. If subjects were unable to provide the name of medication taken these were obtained on the second home visit. Although a crude assessment of SE status (SES) was calculated from the combined levels of education, present occupations and annual income, these data were not analysed as this approach has not been validated in South Africa.

2.2.3 Conventional blood pressure measurements

Trained observers measured BP using a standard mercury sphygmomanometer during two home visits and a clinic visit. These were neither doctors, nor nursing sisters as both are perceived by the community as being in positions of authority and hence may elicit "white-coat" effects. After being trained in the procedure, including being shown pitfalls of BP measurement (positioning of the cuff, positioning of the arm, first estimating systolic BP using a radial pulse measure in order to avoid increasing cuff

pressures too high, detecting auscultatory gaps, releasing valve pressure at the correct speed, using the correct cuff size, etc.), assistants had to demonstrate an ability to perform the procedure on 20 subjects. The study assistants were then tested on their ability to measure BP in two ways. First they were asked to measure BP on a separate group of 20 subjects including patients with hypertension and their readings had to be within 4 mm Hg of a doctors/nursing sister's readings obtained with a stethoscope with two ear pieces. Second, study assistants were asked to watch a video showing a simulated mercury column with Korotkoff sounds where observers were tested on their ability to detect phase I and V sounds under different circumstances including in the presence of a wide auscultatory gap and where phase V Korotkoff was taken as a "muffling" rather than a "disappearance" of sounds (Blood Pressure Measurement, British Medical Journal, BMA House London). To qualify as observers all their readings (n = 20) had to be within 4 mm Hg of the reference standard. Those assistants who failed on the assessment the first time were given more time to practise on subjects and then asked to repeat the tests.

Home visits were conducted 3-to-4 weeks apart and the clinic visit occurred between the two home visits. A standard cuff with a 12 $\times$ 24 cm inflatable bladder was used, but if upper arm circumference exceeded 31 cm, larger cuffs with a 15 $\times$ 35 cm inflatable bladder were used. After 10 minutes of rest in the sitting position, five consecutive BP readings were taken 30 to 60 seconds apart with the subject in a sitting position, followed by a pulse rate count. The cuff was deflated at approximately 2 mm Hg per second and phase I (systolic) and phase V (diastolic) BP recorded to the nearest 2 mm Hg according to the recommendations of the European Society of Hypertension (O'Brien et al 2003). The mean of the five measurements taken at the first home visit was recorded as the home BP. Between the two home visits subjects were invited to the School of Physiology Hypertension Clinic where the same observers, following the same procedure as the first home visit, measured the subject's blood pressure under

comfortable surroundings. The average of the five readings was taken as the office (conventional) BP. Office rather than home measurements were used to define the presence or absence of hypertension in untreated subjects.

In the present study quality control of conventional BP assessments was assessed as previously described (Kuznetsova et al 2002). Only 0.23% of visits had fewer than the planned BP recordings. The frequency of identical consecutive recordings was 1.15% for systolic BP and 2.08% for diastolic BP. The occurrence of BP values recorded as an odd number was 0.02 %. Of the 8722 systolic and diastolic BP readings, 26% ended on a zero (expected =20%). A diagnosis of hypertension was made if subjects were receiving antihypertensive therapy and/or if the average of the mean values for the clinic readings was ≥140/90 mm Hg.

2.2.4 Anthropometric Measurements

Body height and weight were measured during the clinic visit by a trained observer. Height and weight were measured with the participants standing and wearing indoor clothes with no shoes. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Body surface area in meters^2 (m^2) was calculated as (0.0001) x (71.84) x (weight in kg)$^{0.425}$ x (height in cm)$^{0.725}$.

2.2.5 Blood measurements

Blood samples were obtained on the day of the clinic visit and sent to the South African National Health Systems Laboratories (NHSL) to perform a full blood count and differential count, to measure urea, creatinine and electrolyte concentrations, to assess liver function (from alanine transaminase, aspartate transaminase, gamma glutamyl transferase, alkaline phosphatase, albumin, total protein and plasma albumin, total bilirubin, and conjugated and unconjugated bilirubin concentrations) and plasma urate

concentrations, to obtain a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and TG concentrations), a blood glucose measurement, an HbA1c and an FSH in females. These data were used to identify medical conditions and syndromes. A “spot” urine analysis was also performed to screen for major clinical conditions, such as diabetes mellitus and renal pathology. The NHSL was utilised for blood measurements to ensure reproducibility and reliability as these laboratories have been accredited as fulfilling all criteria of “good laboratory practise”. In those subjects without a prior history of diabetes mellitus, an HbA1c rather than a fasting blood glucose concentration was utilised in the APOGH study to assess blood glucose control.

2.2.6 Echocardiography.

Echocardiographic measurements were performed using previously described methods (Sareli et al 2001). Briefly, two-dimensional guided M-mode echocardiography was performed using a pulse color Doppler Hewlett Packard model 5500 recorder coupled to a 2.5 MHz transducer. Data obtained in the short axis view were analyzed according to the American Society of Echocardiography (ASE) convention (Sahn et al 1978). During recordings the transducer was placed perpendicular to the chest wall or pointed slightly inferiorly and laterally at the end of the long axis (Sahn et al 1978). All measurements were recorded on videotape and analyzed off-line by an experienced investigator (CL), who was unaware of the clinical condition of the subjects. The interventricular septal wall thickness (IVS) at end diastole, the posterior wall thickness (PWT) at end diastole and the end diastolic internal dimensions of the left ventricle were measured only when appropriate visualization of both the right and the left septal surfaces was obtained (Sahn et al 1978). Figure 2.2 shows echocardiography being performed and a representative M-mode image. Left ventricular mass was derived according to an anatomically validated formula (Devereux et al 1986) (appendix 1). For comparison purposes with studies that have utilized the ASE convention without

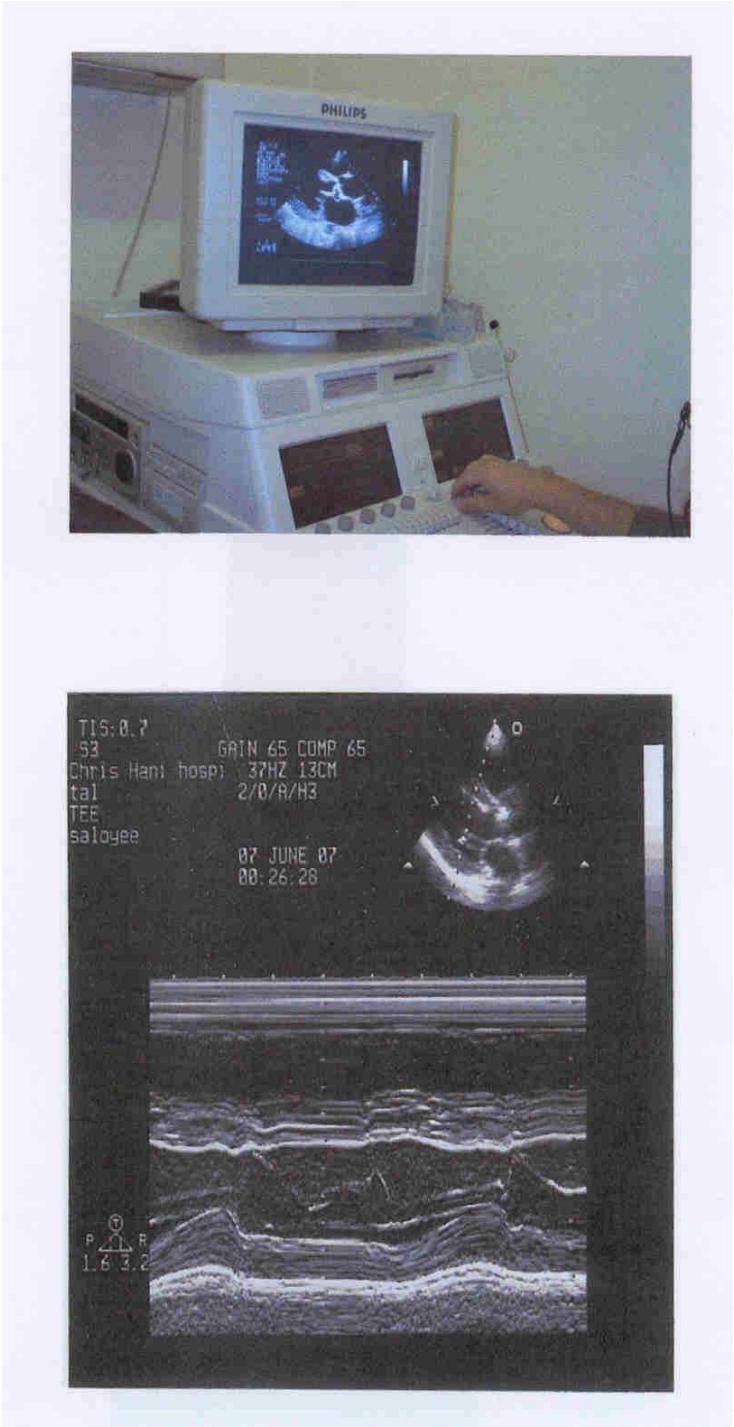


Figure 2.2. Upper panel illustrates the Hewlett Packard model 5500 utilised to assess left ventricular dimensions in the study sample. The lower panel shows an M-Mode image.

corrections for over-estimations, or the Penn convention, LVM was also calculated using these formulae (see appendix 1). Left ventricular relative wall thickness (RWT) was calculated as (LV diastolic posterior wall thickness x2)/LV end diastolic diameter (Ganau et al 1992). Left ventricular mean wall thickness was determined from the mean of LV septal and posterior wall thickness.

2.2.7 Data analysis.

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. Proportions were compared using χ^2-statistics and comparisons between gender groups were performed using an unpaired Student's t-test. To generate a healthy sample of subjects, a total of 258 subjects were excluded, because of hypertension (receiving antihypertensive therapy or a conventional BP≥140/90 mm Hg, n = 188), diabetes (receiving oral or insulin therapy) or impaired blood glucose control (an HbA1c >7%) (n = 35), obesity (body mass index ≥30kg/m^2) (n = 170) or because they had previous or concomitant cardiovascular disease, including coronary heart disease, heart failure, transient ischemic attack, or intermittent claudication (n = 8). The overall number of participants statistically analysed totaled 141.

Relations of LVM to measures of body size were assessed using linear regression analysis. Thresholds for LVM were determined in sex-specific groups from linear regression analysis relating indexed LVM to age. Departure from normality was evaluated by Shapiro-Wilk's statistic (Shapiro and Wilk 1965) and skewness by the computation of the coefficient of skewness, i.e. the third moment about the mean divided by the cube of the standard deviation (Snedecor and Cochram 1980). The normal distribution was used to determine the significance of the coefficient of the skewness (Snedecor and Cochram 1980). For the purposes of comparisons with other population

samples, thresholds for LVM indices were generated for indices with appropriate growth signals only.

2.3 RESULTS

2.3.1 Characteristics of the Participants

Table 2.1 gives the characteristics of the healthy participants by gender. Mean age was 29.2±12.4 years. Women had a higher body mass index than men, with 35/82 women (43%) and 19/59 men (32%) being overweight (BMI≥25kg/m^2). Of the 141 healthy participants, 26 men (18%) and 9 women (6%) were smokers and 22 men (16%) and 13 women (9%) reported alcohol consumption. Among smokers, median tobacco use was 7 cigarettes per day (range, 1–23). Among regular drinkers, median alcohol consumption was 19.8 grams per day (range, 2–117.5). Men had higher values for all measurements of LV structure.

2.3.2 Relationships between left ventricular mass and measures of body size

Figures 2.3-to-2.5 show the relations between LVM and each measure of body size (body weight, body surface area and height)(upper panels) and the relations between LVM normalised to each measure of body size to the first power versus each measure of body size (lower panels). All of the relations essentially fitted a linear function (upper panels). Minimal residual correlations were noted after adjustments of LVM for body surface area (lower panel of Figure 2.4). In contrast, a marked negative relationship between LVM adjusted for body weight to the first power and body weight was noted (Figure 2.3) and a positive relationship between LVM adjusted for height to the first power and height was noted (Figure 2.5).

Table 2.1 Characteristics of the healthy participants

	Men	Women	p-value
Number	59	82	
Age, years	30.1±13.0	28.5±12.0	=0.47
Anthropometic measurements			
Height, cm	170.3± 7.9	158.8± 7.4	<0.0001
Weight, kg	66.4±11.4	60.7±9.5	=0.002
Body mass index, kg/m^2	22.9± 3.6	24.1±3.4	=0.04
Body surface area, m^2	1.77± 0.16	1.62± 0.1	<0.0001
Blood Pressure (mm Hg)			
Systolic	118± 9	112±10	=0.0007
Diastolic	78±8	75± 8	=0.03
Smoking habits (%)	44	11	<0.0001
Alcohol intake (%)	37	16	=0.02
Left ventricular (LV) measurements			
End diastolic diameter (cm)	4.96± 0.45	4.51± 0.43	<0.0001
Posterior wall thickness (end diastole)	0.98± 0.10	0.90± 0.07	<0.0001
Septal wall thickness (end diastole)	1.01± 0.12	0.93± 0.09	<0.0001
LV mass (g)	180±38	138±27	<0.0001
LV mass index (g/m^2)	102±20	85±16	<0.0001
LV mass index (g/m)	106±22	87±17	<0.0001
LV mass index ($g/m^{2.7}$)	43±10	40± 8	=0.028
LV RWT	0.40± 0.05	0.40± 0.05	=0.71

Values are mean ± SD or number (%). P-values are comparisons between men and women.

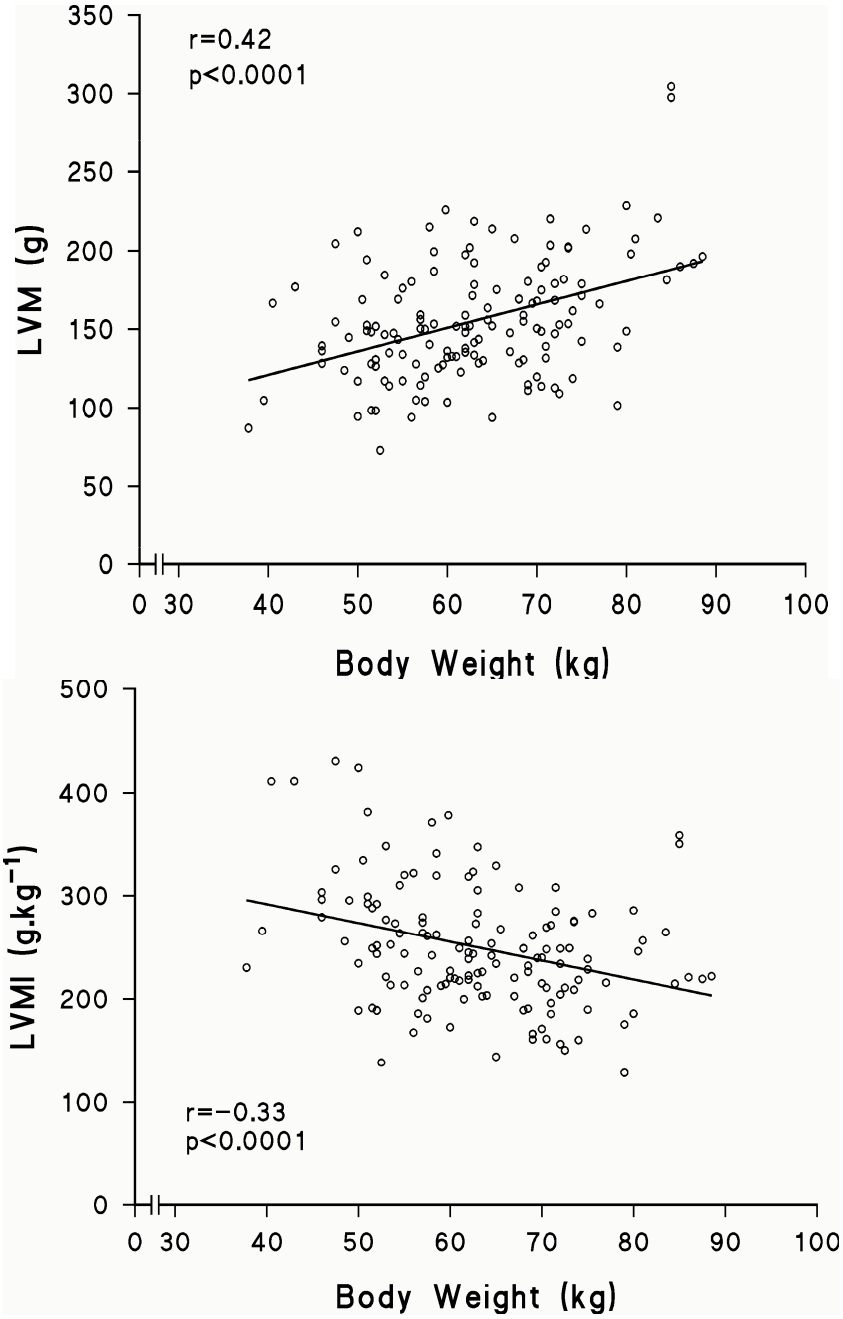


Figure 2.3. Relationship between left ventricular mass (LVM) and body weight (upper panel) and between LVM normalised to body weight to the first power and body weight (lower panel). Correlation coefficients for the relationships are indicated in the figures.

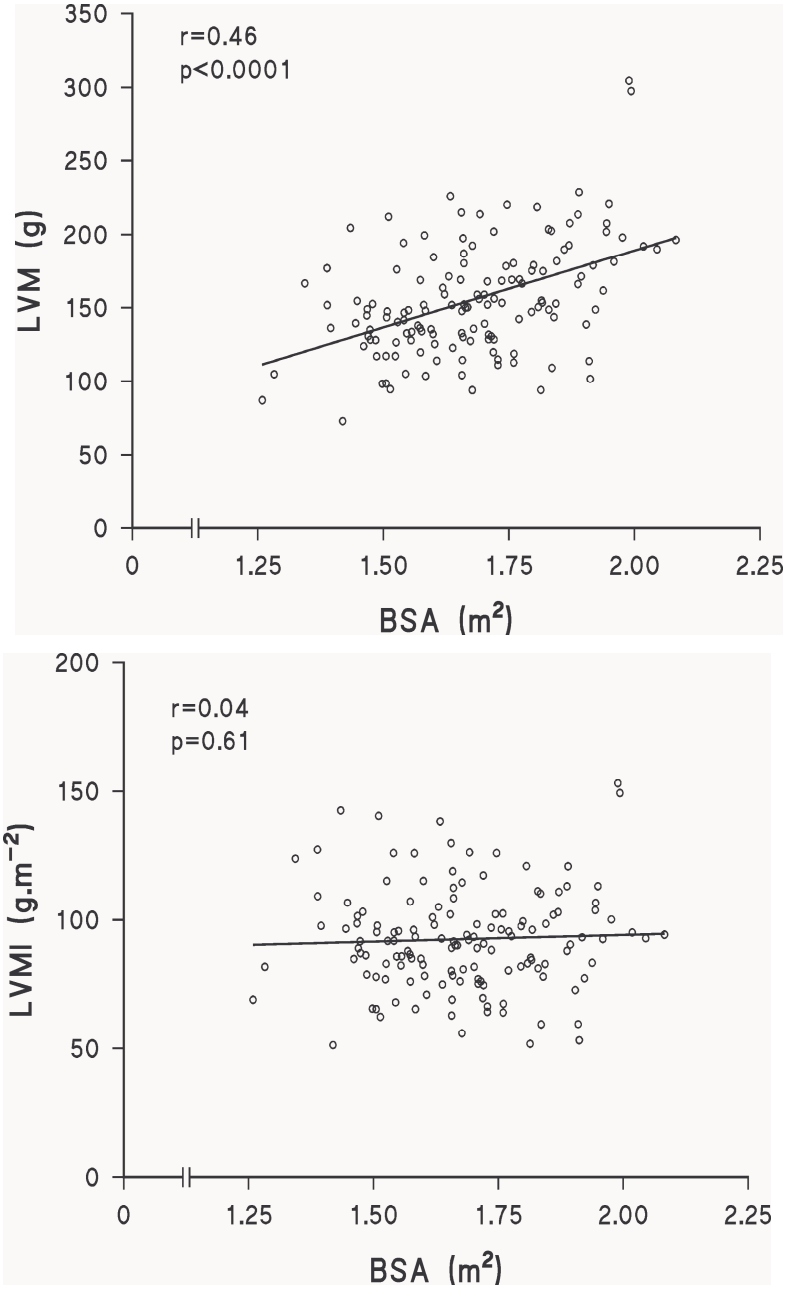


Figure 2.4. Relationship between left ventricular mass (LVM) and body surface area (upper panel) and between LVM normalised to body surface area to the first power and body surface area (lower panel). Correlation coefficients for the relationships are indicated in the figures.

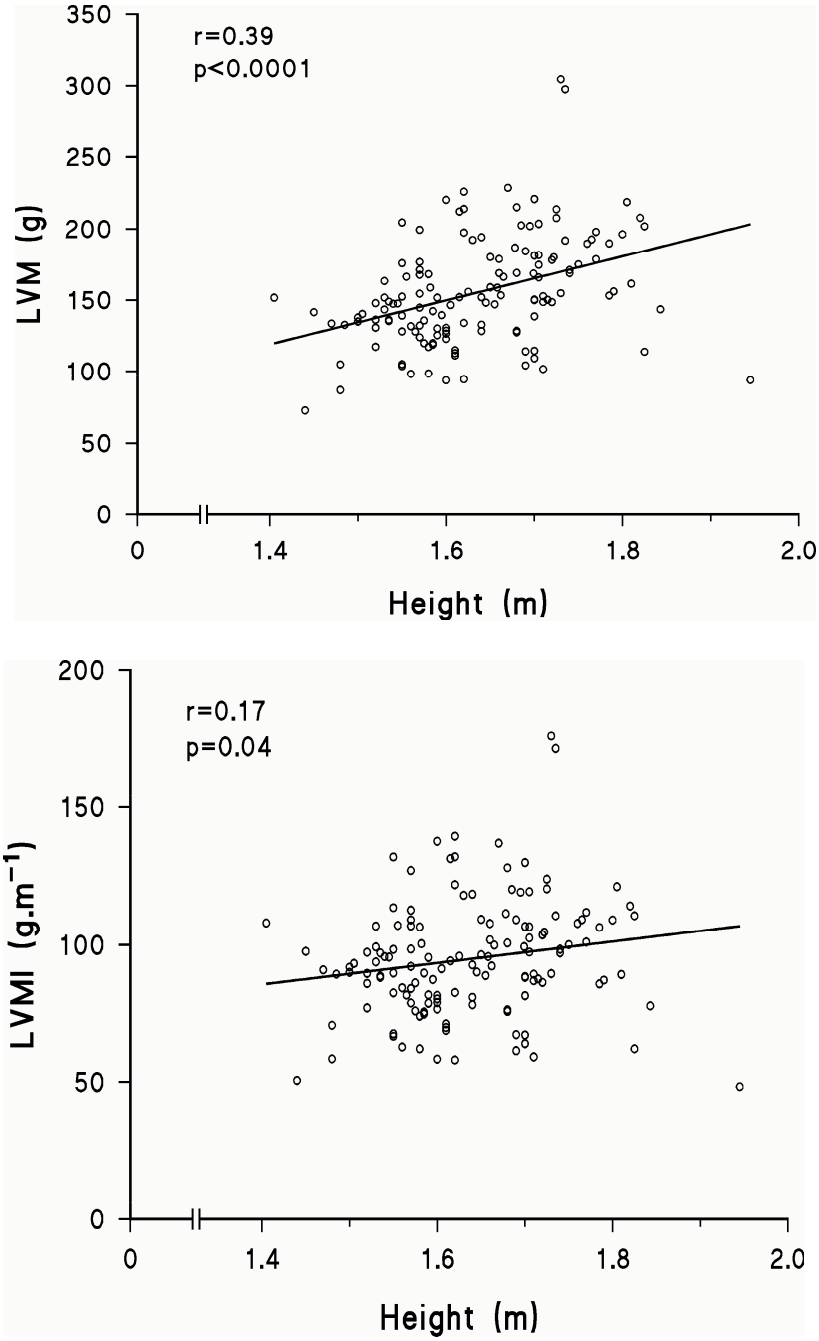


Figure 2.5. Relationship between left ventricular mass (LVM) and height (upper panel) and between LVM normalised to height to the first power and height (lower panel). Correlation coefficients for the relationships are indicated in the figures**.**

2.3.3 Impact of adjustments of LVM for allometric signals generated in other populations.

When adjusting for allometric signals generated in other population groups (body surface area$^{1.5}$ and height$^{2.7}$ (Lauer et al 1994, de Simone et al 1992, 1995), inverse relations were noted between adjusted LVM and either body surface area or height (Figures 2.6-2-7). Thus, allometric signals generated in other population groups markedly over-adjusted for LVM in the present community sample.

2.3.4 Distribution of left ventricular mass

Figure 2.8 shows the distributions of LVM and LVM indexed for body surface area. The distributions departed from normality and were positively skewed ($p<0.001$). The coefficients of skewness were 0.81 for LVM and 0.50 for LVM indexed for body surface area.

2.3.5 Proposal for diagnostic thresholds for left ventricular mass index

To determine diagnostic thresholds of LVM index for men and women in this community, the 95th prediction bands (Figure 2.9) for the approximate mean age of the participants (30 years) was rounded downwards to the nearest value ending in zero, or integer for LVM indexed for body surface area. This procedure yielded the following thresholds: 134 g/m^2 for LVM indexed for body surface area for men and 112 g/m^2 for LVM indexed for body surface area for women. LVM index tended to increase with age, although this did not reach statistical significance (Figure 2.9). Per decade of life, the aforementioned thresholds may therefore be altered by approximately 1.2 g/m^2 for LVM

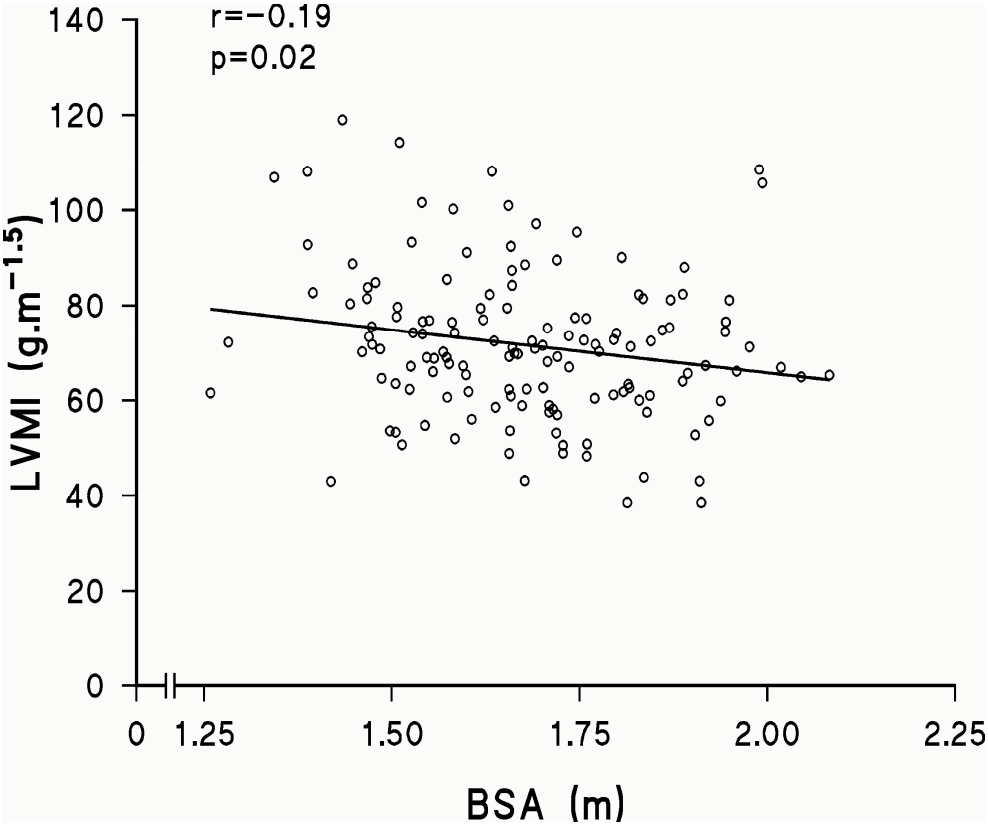


Figure 2.6. Relationship between left ventricular mass (LVM) normalised to body surface area$^{1.5}$ and body surface area. The correlation coefficient for the relationship is indicated in the figure.

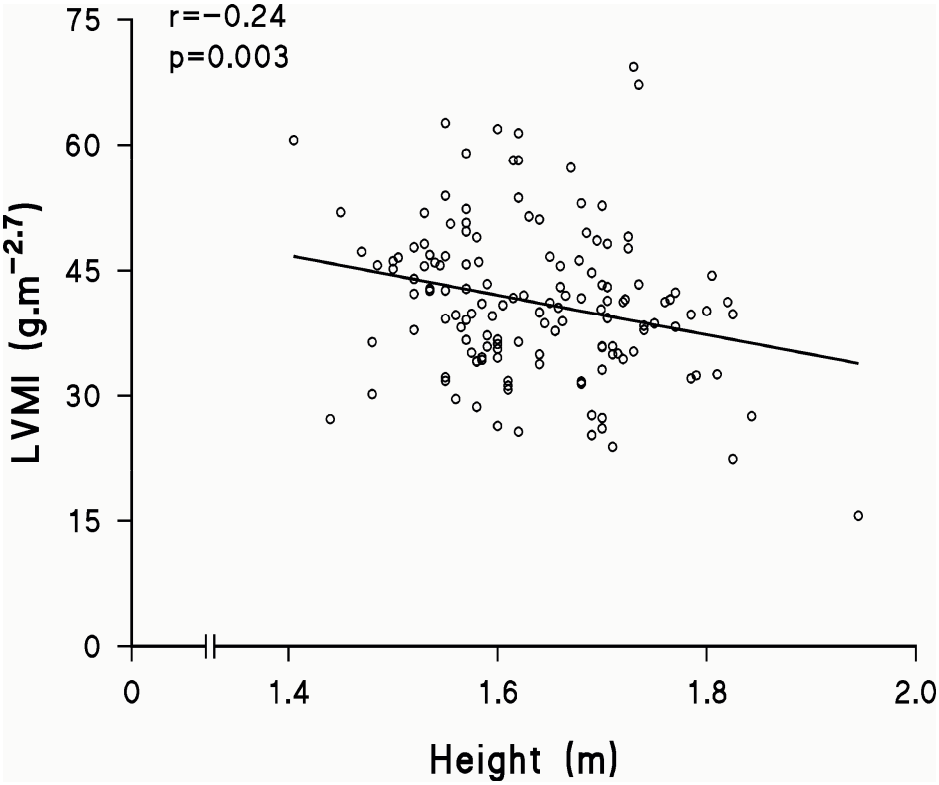
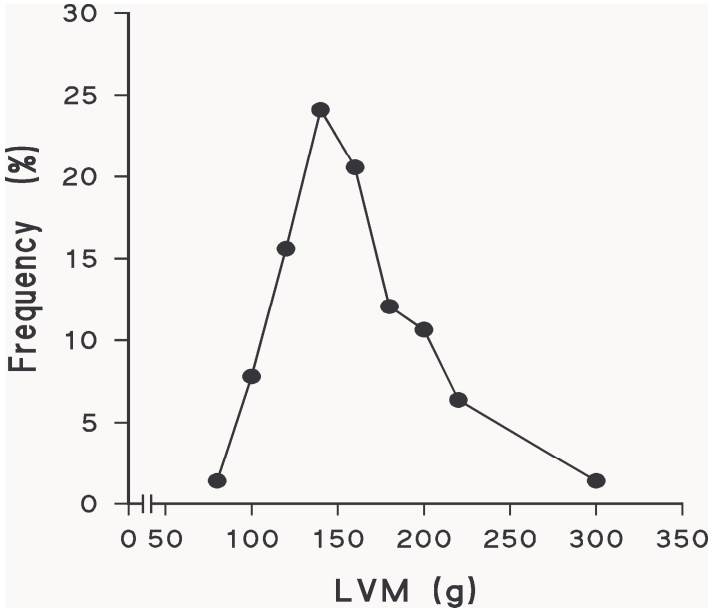


Figure 2.7. Relationship between left ventricular mass (LVM) normalised to height$^{2.7}$ and height. The correlation coefficient for the relationship is indicated in the figure.



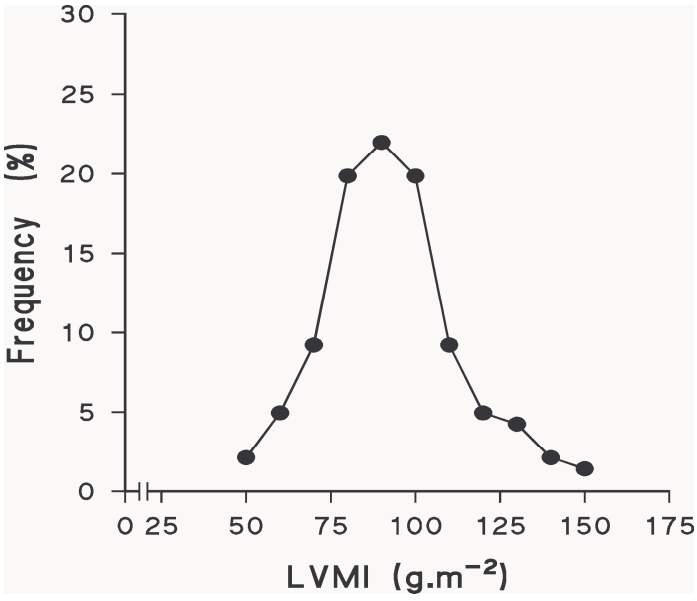


Figure 2.8. Distributions of left ventricular mass (LVM) and LVM indexed for body surface area in healthy subjects.

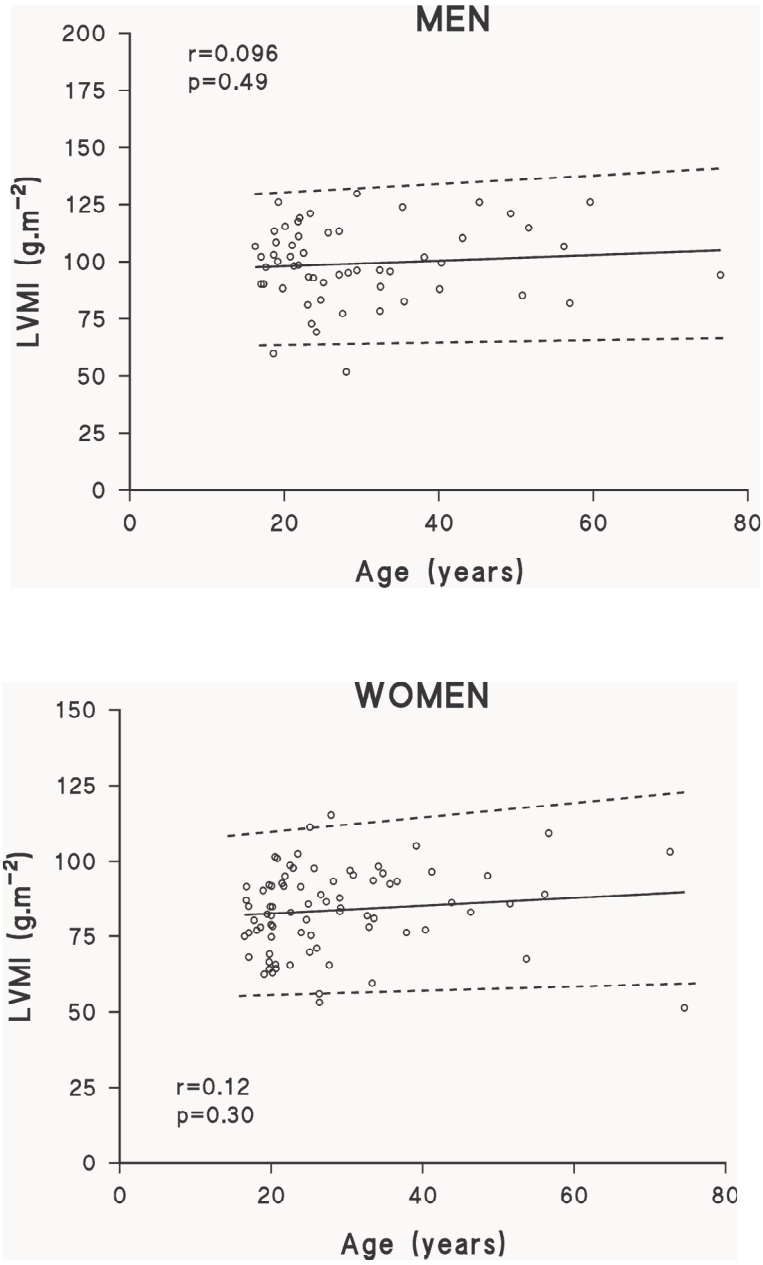


Figure 2.9. Sex-specific relations of left ventricular mass (LVM) indexed for body surface area with age in study subjects. Each panel shows the regression line and the 95% prediction bands for mean and individual values of LVM index.

indexed for body surface area for men, and 1.4 g/m^2 for LVM indexed for body surface area for women.

2.3.6 Comparison of diagnostic thresholds with other populations

Table 2.2 shows thresholds for LVM indexed to body surface area obtained in the present population sample and in those reported on for other population groups. Thresholds defined for LVM calculated from the American Society of Echocardiograpy convention (both corrected for LVM overestimations [Devereux et al 1986] and uncorrected) and the Penn convention are shown. These have been included for comparative purpose with other population samples where different methods for calculating LVM have been employed. Irrespective of the method of calculation of LVM, LVM indexed to body surface area was noted to be marginally higher than in studies conducted in other population groups.

2.4 DISCUSSION

The main findings of the present study are as follows. First, in a healthy group of participants of African ancestry living in South Africa, the relationship between LVM and body size appears to differ from that noted in other populations. Unlike other populations where adjusting LVM for power functions of either body surface area (body surface area$^{1.5}$) or height (height$^{2.7}$) is required to eliminate residual relations between LVM and body size, the use of these allometric signals resulted in marked overadjustments of LVM in the present study. The most appropriate index to adjust LVM for body size in the present study was LVM adjusted for body surface area to the first power, which eliminated residual relations between LVM and body size. Second, in the absence of an outcome-driven reference frame for the present population, our study suggests thresholds

Table 2.2. Thresholds for echocardiographic LVM indexed to body surface area as determined from confidence intervals or means and standard deviations (SD) in the present and in other populations.

Study	Population	Threshold	
		Men	Women
Present	African ancestry	168#	140#
		134†	112†
		158*	130*
Levy et al 1987	Caucasian	150#	120#
		131*	100*
Lauer et al 1994	Caucasian	130*	96*
Savage et al 1987	Caucasian	131*	100*
Devereux et al 1984	Caucasian	134*	110*
Chaturverdi et al 1994	Mixed	123†	111†
de Simone et al 1992	Caucasian	117†	105†
de Simone et al 1995	Caucasian	117†	104†

From the ASE criteria without corrections for over-estimation (Devereux et al 1986); † From the American Society of Echocardiography convention; * From the Penn convention. Bold and italix are all data from the Framingham Heart study**.**

for normal LVM indexed to body surface area in this population. Third, in comparison to other population-based studies, the thresholds noted in healthy individuals in the present study for LVM indexed to body surface area are marginally higher than in other population samples (Table 2.2).

Although measurements of LVM using echocardiography have been established as being useful in predicting CVD (Casale et al 1986; Levy et al 1990; Koren et al 1991; Levy et al 1994; Verdecchia et al 1996; Ghali et al 1998; Devereux et al 2004[2]), there has been some debate as to how best to adjust for growth effects on LVM, changes that are of physiological but not pathological relevance. Presently there are several methods to normalize LVM using different measures of body size (height, weight, body surface area)(de Simone et al 1992, Lauer et al 1994, Urbina et al 1995, de Simone et al 1995, Bella et al 1998), but the most appropriate growth signals for LVM appear to be power functions (height$^{2.7}$ and body surface area$^{1.5}$)(de Simone et al 1992, Lauer et al 1994, de Simone et al 1995). Indeed, power functions (height$^{2.7}$ and body surface area$^{1.5}$) appear to elimate residual correlations between LVM and body size (de Simone et al 1992, Lauer et al 1994, de Simone et al 1995). However, studies conducted that define appropriate growth signals for LVM have been conducted in groups of European ancestry. Appropriate growth signals for LVM have not been formally identified in groups of African ancestry.

In the present study conducted in healthy participants of African ancestry, I have demonstrated that indexing LVM for height$^{2.7}$ produces overadjustments of LVM as indicated by inverse correlations between height$^{2.7}$ adjusted LVM and height ($r=-0.24$, $p=0.003$). Similarly, indexing LVM for body surface area$^{1.5}$ produces overadjustments of LVM as indicated by inverse correlations between body surface area$^{1.5}$ adjusted LVM and body surface area ($r=-0.19$, $p=0.04$). These inverse relations between height$^{2.7}$ adjusted LVM and height have been noted in other population groups, but they have been modest at best and consistent with inverse relations between LVM/bodyweight versus body weight relations (de Simone et al 1992). In contrast, in the present study, the inverse

relation between height$^{2.7}$ adjusted LVM and height was distinct and represents a clear overadjustment for body size effects on LVM. Rather, of all the indexes used to-date, indexing LVM for body surface area to the first power was noted to be the most appropriate method of eliminating residual correlations between LVM and body size (Figure 2.4, lower panel).

Unlike the present study, one previous study conducted in 65 men and 99 women of African descent living in Southern Africa (Mauritius) suggested that adjustment of LVM for height to the first power does indeed eliminate the correlation between LVM and height (Jaggy et al 2000). Although in the present study adjustments of LVM for height to the first power reduced the correlation between LVM and height (Figure 2.5, lower panel), this did not eliminate the correlation. Consequently, it is likely that a power function for height is still required to adjust LVM for height effects in the population sampled. However, as the most appropriate height signal in the present population is unlikely to represent a signal previously described for indexing LVM, it has no value when comparing thresholds derived in the present population with thresholds generated in other population samples.

An explanation for the distinct differences in the relationship between LVM and body size in Southern African groups of African descent (this study and Jaggy et al 2000) and in other population groups (de Simone et al 1992, Lauer et al 1994, de Simone et al 1995) should be considered. In both the present and a previous study (Jaggy et al 2000), the mean height of the study subjects was lower than that generally noted to occur in Caucasian and African-American groups. A reduced height but a similar degree of muscularity achieved may significantly modify the relationship between LVM and either height or body surface area. As muscularity was not measured in the present study, this potential explanation remains speculative. Importantly, differences in the degree of adiposity cannot explain the discrepancies in the relationship between LVM and body size in Southern African groups of African ancestry and population groups elsewhere. Indeed, in all studies (this study and Jaggy et al 2000, de Simone et al 1992, Lauer et al 1994, de

Simone et al 1995) obese subjects were excluded from the groups assessed and a similar mean BMI was noted.

Thresholds for LVM have more recently been defined from outcome-based studies. Outcome-based studies have appropriately described thresholds for LVM indexed to height$^{2.7}$. However, as indicated by the present study, height$^{2.7}$ is an inappropriate index for the population studied. Thus, it is important to define thresholds for the present population using appropriate allometric signals. In the absence of outcome-based studies, the present study suggests thresholds for LVM indexed to an appropriate allometric signal, as defined from clinically healthy individuals. Importantly, in the present study, thresholds of LVM index obtained in healthy individuals do not appear to be strikingly greater than those described in largely Caucasian populations (see Table 2.2). However, the fact that the relations between LVM and growth signals are not the same in the present as in other populations, comparing LVM index thresholds obtained in the present with those defined in other population samples, may be a spurious comparison.

In summary the present study provides evidence to suggest that growth signals for LVM in populations of African ancestry living in South Africa are different from other population groups. Further, the present study suggests that thresholds for LVM index in an apparently healthy group of African descent are not strikingly higher than in other population studies.

Chapter 3

Diurnal Blood Pressure Profiles and the Prediction of Left Ventricular Mass Beyond that of Conventional Blood Pressures in Subjects of African Descent

ABSTRACT

Whether an attenuated nocturnal decline in blood pressure (BP) in subjects of African descent translates into a greater left ventricular mass (LVM) independent of conventional BP is uncertain. In the present study, I examined whether ambulatory BP (SpaceLabs, model 90207) is associated with LVM indexed to body surface area (LVMI)(echocardiography) better than or independent of conventional BP and whether diurnal BP profiles determine LVMI in a randomly selected population sample (n=399) of a group of African ancestry. Conventional BP (standardized and non-physician determined) was determined from the mean of 5 measurements. 22% were receiving antihypertensive treatment. Adjustments were made for sex, age, body mass index, non-independence of family members, antihypertensive treatment, and the presence of diabetes mellitus or an HbA1c>7.0%. Neither the ratio of night-to-day BP, nor differences in night-to-day BP were associated with LVMI. After adjustments, conventional, 24-hour, daytime and night-time systolic BP (SBP) were associated with LVMI, with equivalent relations noted for conventional ($r=0.21$, $p<0.0005$) and 24 hour ($r=0.17$, $p<0.005$) SBP and for daytime ($r=0.17$, $p<0.005$) and night-time ($r=0.16$, $p<0.01$) SBP. Diastolic BP was not independently related to LVMI. With conventional BP included as a covariate, neither 24-hour, daytime nor night-time BP were independently associated with LVMI in the whole group. Similar outcomes were noted in untreated subjects. However, in sex-specific analysis, night-time BP was associated with LVMI independent of conventional BP in men ($n=110$, $r=0.21$, $p<0.05$). In conclusion, in persons of African descent, diurnal BP profiles do not contribute to LVMI and neither 24-hour, nor daytime BP predict LVMI beyond conventional BP. However, nocturnal BP may contribute to LVMI in men, but not in women, independent of conventional BP.

3.1 INTRODUCTION

As summarized in chapter one, LVM is a strong independent predictor of CVD (Casale et al 1986; Levy et al 1990; Koren et al 1991; Levy et al 1994; Verdecchia et al 1996; Ghali et al 1998; Devereux et al 2004[2]; Okin et al 2004). Moreover, groups of African ancestry living outside of Africa have a higher LVM than groups of European descent, changes that are independent of conventional BP, fat mass and fat-free mass (Skelton et al 2003, Lorber et al 2003, Kizer et al 2004, Rodriguez et al 2004, Drazner et al 2005). These conventional BP-independent ethnic differences in LVM may translate into an increased prevalence of CVD. However, the exact mechanisms responsible for an increased LVM in groups of African ancestry have not been reported on.

Several cross-sectional studies conducted in Caucasian groups have reported that ambulatory blood pressure is more closely associated with LVM than conventional BP (reviewed by Fagard et al 1995[1], Verdecchia et al 1999, Fagard and Staessen 2002). There are a number of explanations for the differences in the association of conventional and ambulatory BP with LVM. One potential explanation is that unlike conventional BP measurements, ambulatory BP accounts for 24-hour and nocturnal BP loads. In this regard, groups of African descent are thought to have an enhanced 24-hour BP load for any given daytime BP, as they have an attenuated nocturnal decrease in BP (Profant and Dimsdale 1999, Wang et al 2006). However, as studies with small sample sizes, poor quality ambulatory and possibly conventional BP data, and with inconsistent outcomes have addressed the issue of whether attenuated nocturnal decreases in BP translate into an enhanced LVM in groups of African ancestry (Murphy et al 1991, Fumo et al 1992, Chatuvedi et al 1994, Olutade et al 1998, Mayet et al 1998, Palmieri et al 1999, Harshfield et al 2002, Hinderliter et al 2004) this question still remains unanswered. Moreover, none of the studies evaluating the role of nocturnal decreases in BP as a determinant of LVM in groups of African descent have assessed whether indices of nocturnal decreases in BP, 24-hour BP, daytime BP or nocturnal BP predict LVM beyond

that provided by conventional BP. In the present study I therefore assessed the relationship between nocturnal decreases in BP and LVM in a relatively large community-based sample of randomly recruited nuclear families of African descent. I also assessed whether 24-hour BP, daytime BP or nocturnal BP predict LVM either better than or independent of conventional BP in subjects of African ancestry.

3.2 METHODS

3.2.1 Study group, demographic and clinical data, conventional blood pressure measurements and echocardiography.

The community sampled and the sampling approach has been described in full in chapter 2 of the present thesis. Of the 656 subjects recruited for the present study, 399 subjects had high quality echocardiograms (see chapter 2) and 297 subjects had both high quality echocardiograms and 24-hour ambulatory BP values that met pre-specified quality control criteria (see below for description). Demographic and clinical data and conventional BP and echocardiographic measurements were obtained as described in chapter 2.

3.2.2 Ambulatory blood pressure.

On the same day as conventional BP measurements were obtained, 24-hour ambulatory BP monitoring was performed using oscillometric monitors (Spacelabs, model 90207) (see Figure 3.1). Ambulatory monitors were calibrated monthly against a mercury manometer. The non-dominant arm was selected for BP monitoring. The size of the cuff was the same as that used for conventional BP measurements. The monitors were programmed to measure BP at 15-minute intervals from 06:00 to 22:00 h and at 30-minute intervals from 22:00 to 06:00 h. Subjects kept a diary card for the duration of the

recordings to note the time of going to bed in the evening and getting up in the morning. Subjects were also asked to record the time when taking medication in those receiving medication and any times when they either smoked or took caffeine containing or alcoholic beverages. Subjects were asked to pursue their normal daily activities and to keep the cuff arm steady during measurements. Considering the patterns of diurnal activities, daytime and night-time were defined as ranging from 09:00 to 19:00 h and from 23:00 to 05:00 h, respectively. These fixed clock-time intervals were defined in order to eliminate the transition periods (evening and morning) during which BP changes rapidly in most subjects (Thijs et al 1992). On completion of the recording, the data were transferred to a computer for analysis. Intra-individual means of the ambulatory measurements were weighted by the time-interval between successive recordings (Thijs et al 1992). Of the participants enrolled in the study, we discarded 67 from the analysis, because the ambulatory BP measurements did not meet pre-specified quality criteria (more than 20 hours of recordings and more than 10 and 5 readings for the computation of daytime and night-time means respectively). The degree of nocturnal decreases in BP was assessed by expressing data as either the day-night difference or the ratio of night-to-day BP.

3.2.3 Statistical analysis

Database management and statistical analysis were performed using SAS software versions 9.1 (SAS Institute Inc.) The definitions for hypertension and diabetes mellitus or abnormal blood glucose control are provided in chapter 2. LVM was calculated as described in chapter 2. I have previously demonstrated that indexing LVM for body surface area eliminates residual correlations between LVM and body surface area (chapter 2). Moreover, I have shown that alternative indices used to adjust for height or body surface area (height$^{2.7}$ and BSA$^{1.5}$) described in other populations, considerably

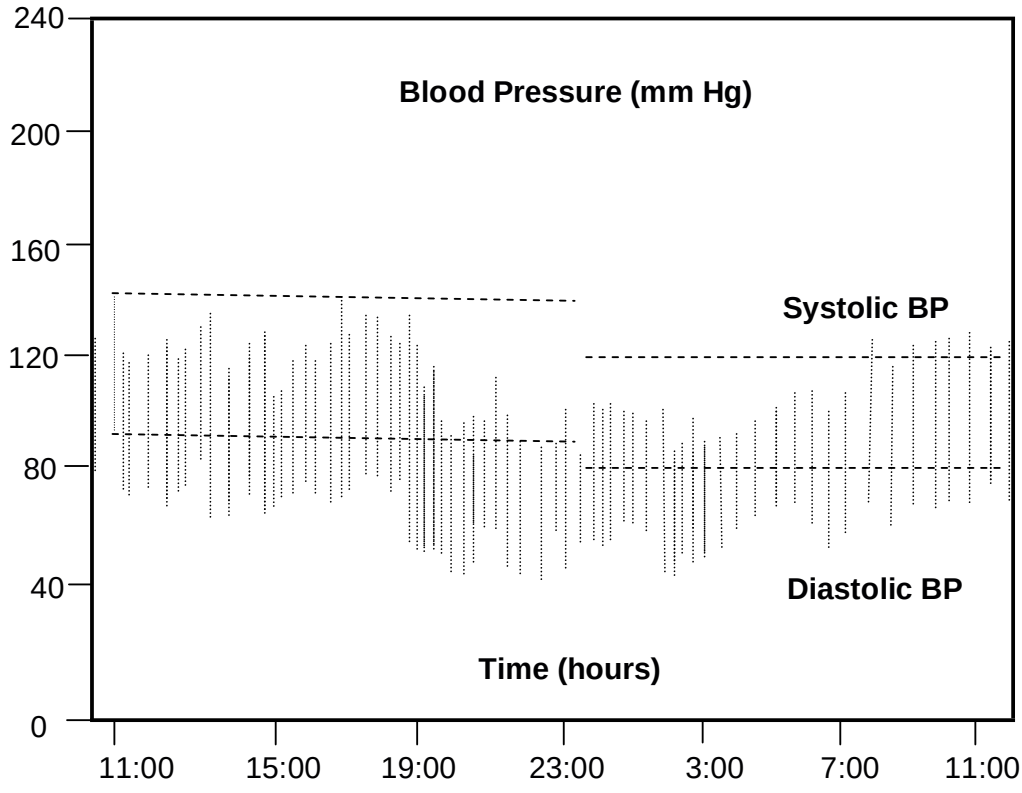


Figure 3.1. Spacelabs model 90207 ambulatory BP monitors (upper panel) and representative data obtained for analysis purposes (lower panel).

overadjust LVM (chapter 2). Consequently, LVM was indexed for body surface area (LVMI) to the first power rather than to power functions described for other population samples. Pearson correlation coefficients for the relationships between BP (or indices of nocturnal decreases in BP) and LVM indexed for body surface area were determined.

Means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. Linear regression analysis with adjustments for sex (except when sex-specific analysis was performed), age, BMI, antihypertensive treatment (except in untreated subjects), and the presence of diabetes mellitus/abnormal blood glucose control, was used to determine the relation between conventional or ambulatory BP and LVMI. For statistical analysis of the relations and the derivation of probability values, further adjustments were made for non-independence of family members. To determine whether 24-hour BP was more closely associated with LVMI that conventional BP, or whether nocturnal BP was more closely associated with target organ effects than daytime BP, adjusted correlation coefficients were compared. When assessing the conventional BP–independent relationship between ambulatory BP and target organ changes, conventional BP was included as an adjustor. Sensitivity analysis was performed in subjects not receiving antihypertensive therapy and in sex-specific groups.

3.3 RESULTS

3.3.1 Population characteristics.

Table 3.1 gives the demographic and clinical characteristics of the subjects. As subjects were not specifically selected as a healthy cohort of the sample, the characteristics of the study sample were different to the cohort of healthy individuals described in chapter 2. The mean age was 43.9±18.1 years. Women had a higher body mass index than men, with 142 women (76%) and 59 men (54%) being overweight or

Table 3.1 Demographic, and clinical characteristics of study subjects

	All subjects	Women	Men
Number	297	187	110
Age (years)	43.9 ± 18.1	42.9 ± 17.5	45.6 ± 19.0
Body Weight (kg)	76.0 ± 17.9	77.3 ± 18.3	73.8 ± 17.0
Body Height (cm)	161.8 ± 8.4	158.0 ± 6.6	168.3 ± 7.0**
BMI (kg/m^2)	29.1 ± 7.1	31.0 ± 7.3	26.0 ± 5.7**
Current antihypertensive medication n,(%)	66 (22)	47 (25)	19 (17)
n,(%) with hypertension	121(41)	77(41)	44(40)
n,(%) with diabetes mellitus	19 (7)	8 (5)	11(10)
Blood pressures			
Conventional (mm Hg)	130±21/84±12	129±22/84±12	132±19/85±11
24-hour (mm Hg)	119±15/73±10	117±16/72±11	121±13*/74±10
Daytime (mm Hg)	123±15/78±10	122±15/77±11	126±13*/79±10
Night-time (mm Hg)	112±17/65±12	111±18/65±12	114±15/66±12
Night-day (mm Hg)	-11±11/-12±9	-10.6±10.4/-12.1±7.9	-12.1±10.8/-12.8±9.6
Night/day	0.9±0.08/0.8±0.1	0.91±0.08/0.84±0.10	0.91±0.09/0.84±0.12

BMI, body mass index; *p<0.05 , ** p<0.001 versus women.

obese (BMI≥25kg/m^2). 41% of the sample was hypertensive, and 7% had type II diabetes mellitus, with more men than women noted to have diabetes mellitus. 22% of the sample were receiving antihypertensive therapy.

Table 3.2 gives the echocardiographic data. As compared to women, men had increased LV dimensions for all parameters.

3.3.2 Relationship between conventional and ambulatory BP.

A strong correlation was noted between conventional systolic BP and 24-hour ($r=0.71$, $p<0.0001$), day ($r=0.69$, $p<0.0001$) and night-time ($r= 0.66$, $p<0.0001$) systolic BP. Moreover, a strong correlation was noted between conventional diastolic BP and 24-hour ($r= 0.61$, $p<0.0001$), day ($r=0.63$, $p<0.0001$) and night-time ($r=0.53$, $p<0.0001$) diastolic BP. Similar relations between conventional and either 24-hour, day or night-time systolic and diastolic BP were noted in both gender groups (men; conventional systolic BP versus 24 hour, $r=0.68$, $p <0.0001$, versus day, $r=0.60$, $p<0.0001$, versus night, $r=0.61$, $p< 0.0001$: women; conventional systolic BP versus 24 hour, $r=0.73$, $p <0.0001$, versus day, $r=0.73$, $p<0.0001$, versus night, $r=0.67$, $p<0.0001$).

3.3.3 Unadjusted associations between BP and LVMI.

LVMI positively correlated with conventional, 24-hour, daytime and night-time systolic and diastolic BP in the whole group (Figure 3.2 and Table 3.3, unadjusted associations) and in untreated subjects (Table 3.4, unadjusted associations). Importantly, no correlations were noted between night-day differences in systolic or diastolic BP or in the night-to-day ratio of systolic and diastolic BP and LVMI (Tables 3.3 and 3.4). No differences in the relationships between conventional BP and LVMI and either 24-hour or daytime BP and LVMI were noted (comparison of correlation coefficients, conventional versus 24-hour or daytime, $p>0.05$). Moreover, no differences in the relationships

Table 3.2. Echocardiographic characteristics of study subjects.

	All subjects	Women	Men
	297	187	110
LVED diameter (cm)	4.77±0.52	4.63±0.49	5.00±0.47*
LVED posterior wall thickness (cm)	0.98± 0.13	0.96±12	1.02±0.15*
LVED septal thickness (cm)	1.03±0.16	1.00±0.14	1.07±0.17*
LV mass (g)	175±52	161±43	199±57*
LV mass index (g/m^2)	98±26	92±23	109±26*

LV, left ventricle; LVED, LV end diastolic. * $p<0.001$ versus women.

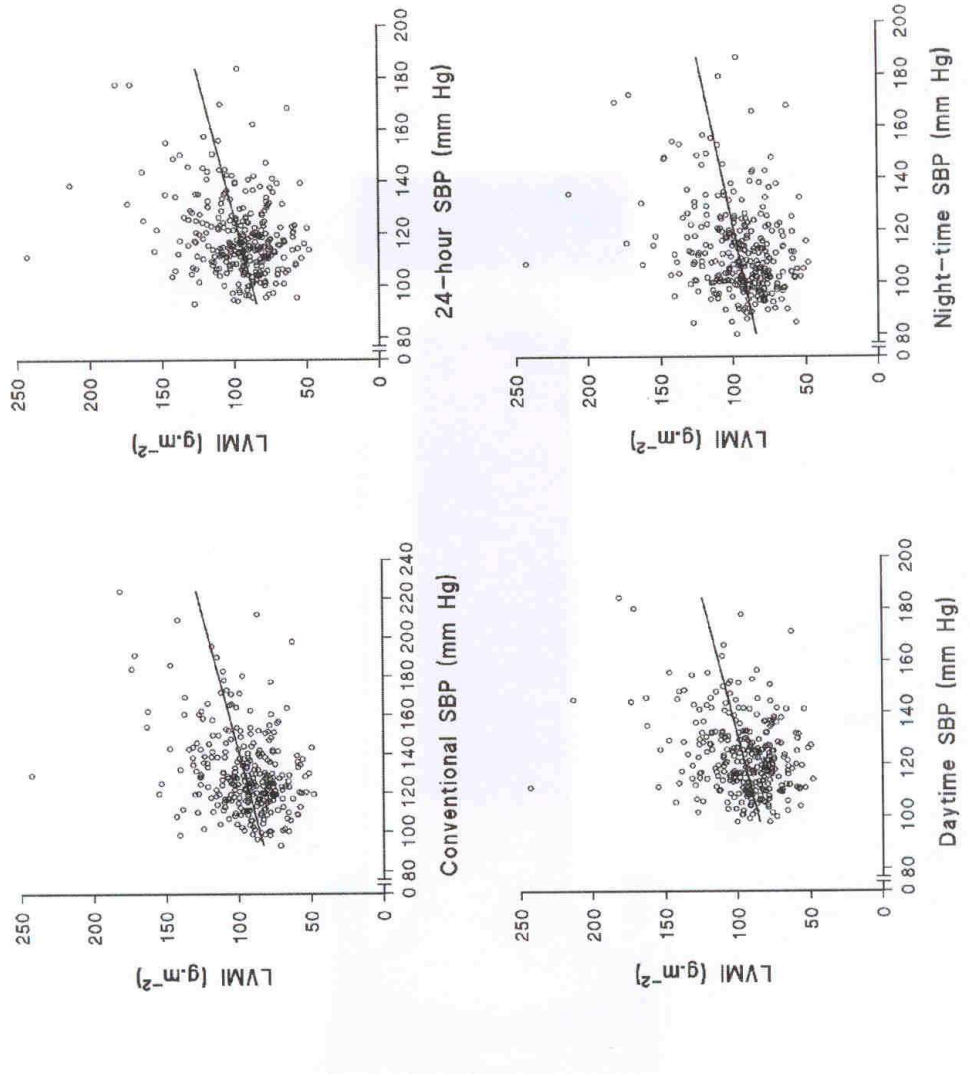


Figure 3.2. Relationships between conventional, 24-hour, daytime and night-time systolic blood pressure (SBP) and left ventricular mass index (LVMI)(g/m^2) in South Africans of African descent. Correlation coefficients are shown in Table 3.3.

Table 3.3. Correlations between blood pressure and left ventricular mass index in all study subjects.

	Systolic BP		Diastolic BP	
	Correlation coefficients (r)	p value	Correlation coefficients (r)	p value
Unadjusted correlations with left ventricular mass index (n=297)				
Conventional BP	0.31	<0.0001	0.14	=0.015
24-hour BP	0.27†	<0.0001	0.13†	=0.028
Daytime BP	0.27†	<0.0001	0.11†	=0.058
Night-time BP	0.26#	<0.0001	0.15#	=0.009
Night-day	0.05	0.42	0.08	=0.20
Night/day	0.08	0.16	0.09	=0.14
Adjusted* correlations with left ventricular mass index (n=297)				
Conventional BP	0.21	<0.0005	0.07	=0.27
24-hour BP	0.17†	<0.005	0.02	=0.82
Daytime BP	0.17†	<0.005	0.02	=0.81
Night-time BP	0.17#	=0.007	0.05	=0.51
Night-day	-0.005	=0.99	0.03	=0.57
Night/day	-0.0004	=0.99	0.02	=0.73

* adjusted for sex, age, body mass index, antihypertensive treatment and the presence of diabetes mellitus/abnormal blood glucose control (+ for 24-hour BP in indexes of nocturnal decreases in BP). Probability values were calculated with additional adjustments for non-independence of family members. # p>0.05 vs daytime values, † p>0.05 vs conventional BP values.

Table 3.4. Correlations between blood pressure and left ventricular mass index in untreated subjects only.

	Systolic BP		Diastolic BP	
	Correlation coefficients (r)	p value	Correlation coefficients (r)	p value
	Unadjusted correlations with left ventricular mass index (n=231)			
Conventional BP	0.35	<0.0001	0.24	=0.0003
24-hour BP	0.34†	<0.0001	0.22†	=0.0009
Daytime BP	0.36†	<0.0001	0.21†	=0.001
Night-time BP	0.31#	<0.0001	0.22#	=0.001
Night-day	-0.03	0.67	0.04	=0.60
Night/day	0.02	0.81	0.06	=0.37
	Adjusted* correlations with left ventricular mass index (n=231)			
Conventional BP	0.29	<0.0001	0.17	=0.02
24-hour BP	0.25†	=0.0002	0.09	=0.19
Daytime BP	0.26†	<0.0001	0.09	=0.19
Night-time BP	0.22#	<0.002	0.10	=0.13
Night-day	-0.05	=0.44	0.03	=0.77
Night/day	-0.05	=0.49	0.01	=0.99

*****adjusted for sex, age, body mass index, and the presence of diabetes mellitus/abnormal blood glucose control (+ for 24-hour BP in indexes of nocturnal decreases in BP). Probability values were calculated with additional adjustments for non-independence of family members. # p>0.05 vs daytime values † p>0.05 vs conventional BP values.

between daytime BP and LVMI and night-time BP and LVMI were noted (comparison of correlation coefficients, daytime versus night-time, $p>0.05$) (Figure 3.2 and Tables 3.3 and 3.4).

3.3.4 Adjusted associations between BP and target organ changes.

Tables 3.3 (all subjects) and 3.4 (untreated subjects) also summarize the correlation coefficients between BP and LVMI after adjusting for sex, age, BMI, antihypertensive treatment (Table 3.3 only) and the presence of diabetes mellitus/abnormal blood glucose control, with non-independence of family members include as an adjustor when determining probability values, and 24-hour BP included as an adjustor when evaluating relationships between indexes of nocturnal decreases in BP and LVMI. Both conventional and ambulatory systolic BP were independently associated with LVMI. However, diastolic BP was not independently associated with LVMI. Conventional BP correlated equally as well with LVMI as 24-hour or daytime BP (comparison of correlation coefficients, conventional versus 24-hour or daytime, $p>0.05$). Daytime systolic BP correlated equally as well with LVMI as night-time systolic BP (comparison of correlation coefficients, daytime versus night-time, $p>0.05$). No associations were noted between night-day differences in BP or night-to-day ratio of BP and LVMI.

3.3.5 Adjusted associations between BP and target organ changes in sex-specific groups.

Table 3.5 summarizes the correlation coefficients between BP and LVMI in sex-specific groups after adjusting for age, BMI, antihypertensive treatment and the presence of diabetes mellitus/abnormal blood glucose control, with non-independence of family members include as an adjustor when determining probability values, and 24-hour BP

included as an adjustor when evaluating relationships between indexes of nocturnal decreases in BP and LVMI. Both conventional and ambulatory systolic BP were independently associated with LVMI in women. However, in men, only nocturnal BP was independently associated with LVMI. Diastolic BP was not independently associated with LVMI in either group.

In women conventional BP correlated equally as well with LVMI as 24-hour or daytime BP (comparison of correlation coefficients, conventional versus 24-hour or daytime, $p>0.05$). Moreover, in women, daytime systolic BP correlated equally as well with LVMI as night-time systolic BP (comparison of correlation coefficients, daytime versus night-time, $p>0.05$). Although in men nocturnal BP, but neither conventional nor daytime BP were associated with LVMI, no differences were noted in the correlation coefficients between night-time BP and LVMI and conventional BP and LVMI ($p=0.23$) or between night-time BP and LVMI and daytime BP and LVMI ($p=0.50$). No associations were noted between night-day differences in BP or night-to-day ratio of BP and LVMI in either women or men.

3.3.5 Conventional BP-independent relationship between ambulatory BP and LVMI.

Figure 3.3 summarizes the relationships between 24-hour, daytime or night-time systolic and diastolic BP and LVMI after adjusting for sex, age, BMI, antihypertensive treatment and the presence of diabetes mellitus/abnormal blood glucose control, as well as conventional BP, with non-independence of family members include as an adjustor when determining probability values. Neither 24-hour, daytime, nor night-time systolic or diastolic BP were associated with LVMI independent of conventional BP.

Table 3.5. Correlations between blood pressure and left ventricular mass index in sex-specific groups.

	Systolic BP		Diastolic BP	
	Correlation coefficients (r)	p value	Correlation coefficients (r)	p value
Adjusted* correlations with left ventricular mass index in women (n=187)				
Conventional BP	0.31	<0.0001	0.16	=0.04
24-hour BP	0.17†	=0.022	0.03	=0.72
Daytime BP	0.20†	<0.007	0.05	=0.47
Night-time BP	0.12#	=0.11	0.03	=0.70
Night-day	-0.11	=0.12	-0.02	=0.68
Night/day	-0.10	=0.17	-0.03	=0.62
Adjusted* correlations with left ventricular mass index in men (n=110)				
Conventional BP	0.07	=0.41	-0.07	=0.49
24-hour BP	0.18†	=0.07	0.04	=0.72
Daytime BP	0.14†	=0.17	0.004	=0.97
Night-time BP	0.23#	=0.02	0.09	=0.37
Night-day	0.14	=0.17	0.10	=0.33
Night/day	0.18	=0.21	0.08	=0.45

*adjusted for age, body mass index, and the presence of diabetes mellitus/abnormal blood glucose control (+ for 24-hour BP in indexes of nocturnal decreases in BP). Probability values were calculated with additional adjustments for non-independence of family members. # p>0.05 vs daytime values † p>0.05 vs conventional BP values.

3.3.6 Conventional BP-independent relationship between ambulatory BP and LVMI in sex-specific groups.

Figure 3.4 summarizes the relationships obtained in sex-specific groups between 24-hour, daytime or night-time systolic and diastolic BP and LVMI after adjusting for age, BMI, antihypertensive treatment and the presence of diabetes mellitus/abnormal blood glucose control, as well as conventional BP, with non-independence of family members include as an adjustor when determining probability values. In men, although neither 24-hour nor daytime systolic or diastolic BP were associated with LVMI independent of conventional BP, night-time systolic BP ($r=0.21$, $p<0.05$), but not night-time diastolic BP was independently associated with LVMI. In women, no conventional BP-independent relationship between ambulatory BP and LVMI was noted. In men, sensitivity analysis conducted in untreated subjects also showed a conventional BP-independent relationship between night-time systolic BP ($p<0.03$) and LVMI. Comparisons of the regression relations between daytime and night-time systolic BP showed no differences in these relations in men ($p=0.37$ for comparisons of regression relations).

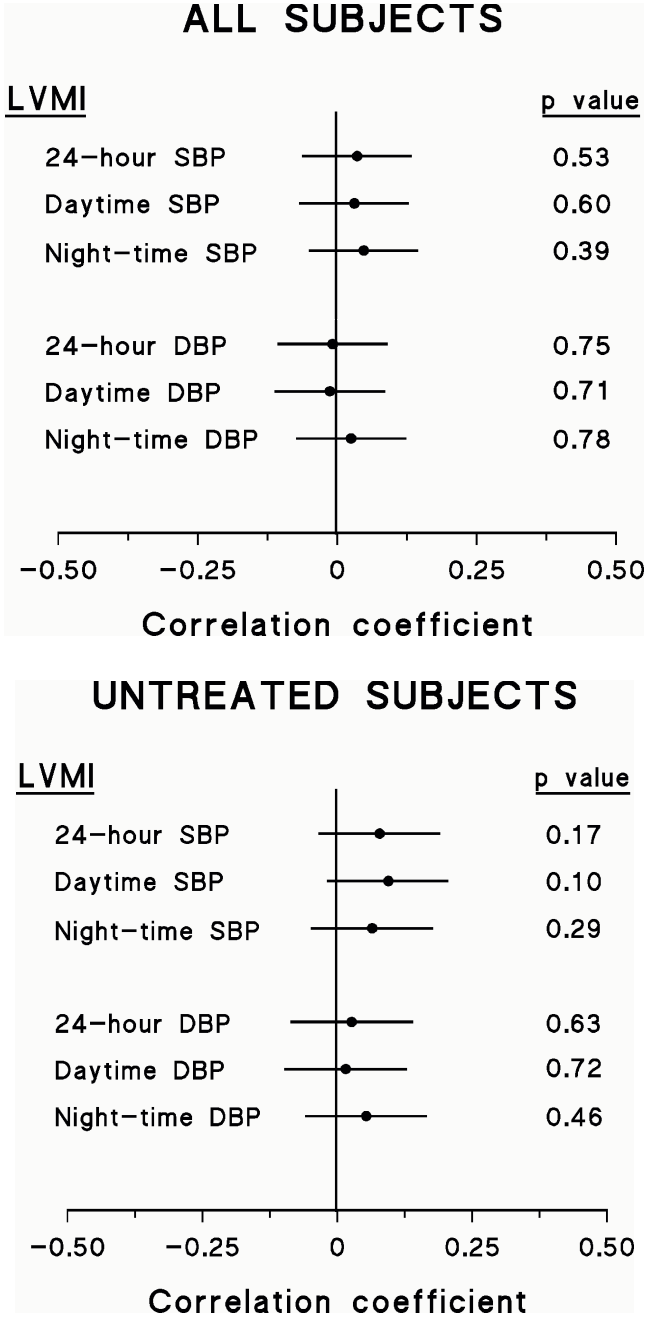


Figure 3.3. Conventional BP-independent relationships between left ventricular mass indexed to body surface area (LVMI) and either 24-hour or daytime systolic (SBP) or diastolic (DBP) blood pressure in all subjects and in untreated subjects as indicated by partial correlation coefficients and 95% confidence intervals. The relationships were adjusted for conventional BP, sex, age, body mass index, antihypertensive treatment (in all subjects), and the presence of diabetes mellitus/abnormal blood glucose control. Probability values were obtained with an additional adjustment for non-independence of family members.

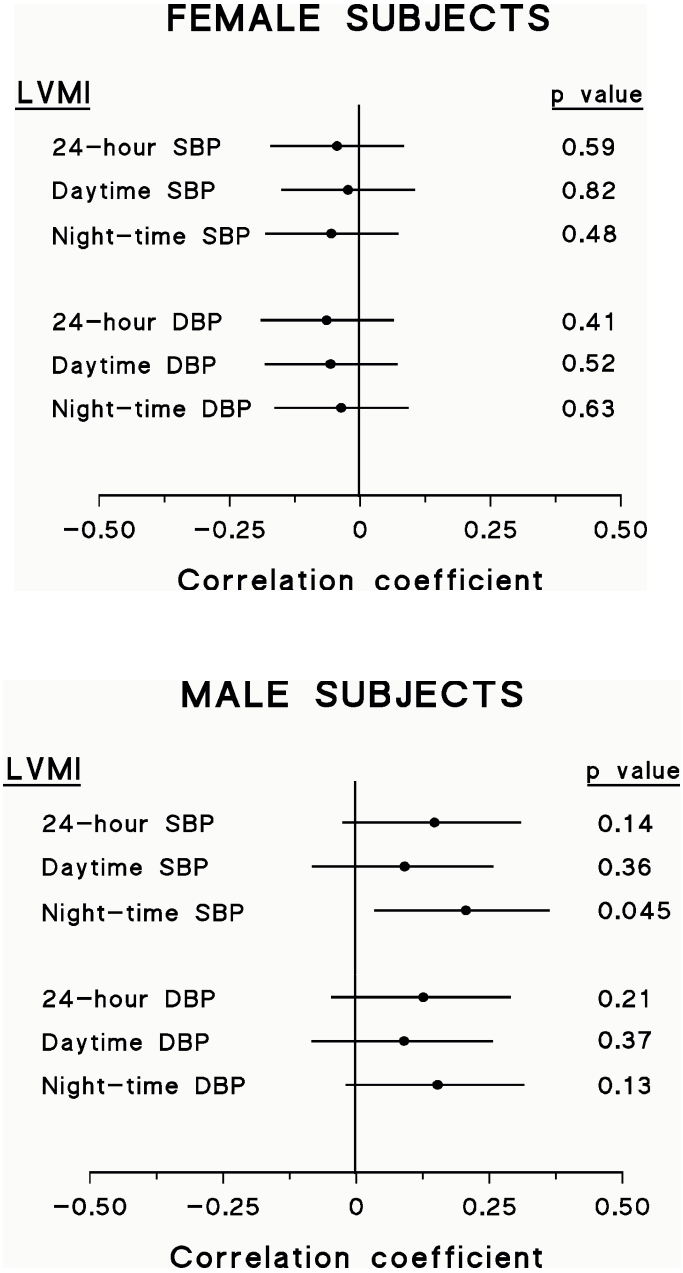


Figure 3.4. Conventional BP-independent relationships between left ventricular mass indexed to body surface area (LVMI) and either 24-hour or daytime systolic (SBP) or diastolic (DBP) blood pressure in sex-specific groups as indicated by partial correlation coefficients and 95% confidence intervals. The relationships were adjusted for conventional BP, age, body mass index, antihypertensive treatment (in all subjects), and the presence of diabetes mellitus/abnormal blood glucose control. Probability values were obtained with an additional adjustment for non-independence of family members.

3.4 DISCUSSION

The main findings of the present study conducted in a large, randomly selected population sample of African ancestry living in Africa with a high frequency of obesity (~40%) and both treated (~22%) and untreated (~18%) hypertension, where conventional, 24-hour, daytime and night-time BP were all associated with LVM index independent of confounders, were as follows. Indexes of nocturnal decreases in BP were not associated with LVM index; daytime BP was as closely associated with LVM index as was nocturnal BP; conventional BP was as closely associated with LVM index as 24-hour, daytime and night-time BP, and ambulatory BP was not associated with LVM index independent of conventional BP. However, on sensitivity analysis conducted in sex-specific groups, night-time BP was associated with LVM index independent of conventional BP in men, but not in women.

Previous studies conducted exclusively in subjects of European or Asian descent have indicated that an attenuated nocturnal decrease in BP or nocturnal BP *per se* is associated with lacunar infarcts (Yamamoto et al 1998), cardiovascular outcomes in the elderly with isolated systolic hypertension (Staessen et al 1999), cardiovascular outcomes in hypertensives in general (Verdecchia et al 1994, Zweiker et al 1994), cardiovascular outcomes in the general population (Ohkubo et al 1997, Kikuya et al 2005) and vascular events in type II diabetes mellitus (Nakano et al 1998) independent of conventional BP values. However, in groups of African descent, there are few studies that have evaluated the role of diurnal variations in BP as potential determinants of cardiovascular target organ effects or outcomes.

In general, studies evaluating a potential role of diurnal variations in BP in groups of African descent have focussed on target organ effects, such as LVM. However, in this regard, there is no consensus as to the role of diurnal variations in BP on LVM in groups of African descent as these studies have been conducted in small samples, with disparate study designs and definitions of day and night BP and have had inconsistent

outcomes. Murphy et al (1991) and Fumo et al (1992) observed a greater night-time BP and a higher LVM in small study samples (22-44) of subjects of African ancestry. In 39 African-American men and 49 African-American women, in comparison to a group of subjects of European ancestry (n=83), ethnic differences in LV wall thickness were abolished by adjustments for sleep BP (Hinderliter et al 2004). Moreover, in 46 hypertensives of African descent, nocturnal decreases in systolic BP were associated with LVM index, but not in a group of 46 hypertensives of European ancestry (Mayet et al 1998). A greater frequency of subjects with an attenuated nocturnal decrease in BP was noted in subjects of African descent with concentric LV remodelling (Olutade et al 1998) and night-time systolic BP and indices of nocturnal decreases in BP were associated with concentric LV hypertrophy (El-Gharbawy et al 2001). In contrast, Chaturvedi et al (1994), demonstrated in 78 men and 89 women of African descent that daytime, but not night-time BP was associated with LVM index. Moreover, in 94 African-Americans of a mean age of 14 years, neither day nor night BP was associated with LVM index (Harshfield et al 2002) and in a mixed group of Caucasian and African-Americans, day-night differences in BP were not associated with LVM (Palmieri et al 1999). The present study conducted in a relatively large population sample (n=297) provides evidence to suggest that nocturnal BP may predict LVM index beyond conventional BP in men, but not in women.

The relationship between indices of nocturnal decreases in BP and LVM has been extensively studied in groups of European ancestry. In this regard, there is also considerable controversy as to whether an attenuated nocturnal decrease in BP is associated with LVM, with some studies showing a relationship (Verdecchia et al 1990, Verdecchia et al 1992, Schmieder et al 1995), whilst others have reported on no relationship (Schulte et al 1993, Boley et al 1997, Roman et al 1997). These discrepancies may be attributed to a sex-specific effect, where nocturnal decreases in BP affect LVM in women (Verdecchia et al 1992, Schmieder et al 1995). In contrast, in the present study I demonstrated a conventional BP-independent relationship between nocturnal BP and LVM index in males as opposed to females. The discrepancy between

this and previous studies (Verdecchia et al 1992, Schmieder et al 1995) may relate to the considerably higher sample size employed in the present study as compared to previous studies or that different ethnic groups were studied. Importantly, however, the results of the present study provide substantially stronger evidence to indicate that nocturnal decreases in BP are not related to LVM index, but that nocturnal BP may provide information beyond conventional BP when predicting LVM index in males.

In the present study ambulatory BP was not more closely associated with LVM index than conventional BP. A number of previous studies have shown significantly better correlations of ambulatory BP values with LVM index than conventional BP (reviewed by Fagard et al 1995[1], Verdecchia et al 1999, Fagard and Staessen 2002). In this regard there are a number of explanations for the discrepancy between the impact of ambulatory and conventional BP on LVM including the lack of standardization of conventional BP measurements and inappropriate quality control (Fagard et al 1995[1], Fagard and Staessen 2002). In the present study, conventional BP was measured by a single trained nursing sister, thus avoiding the potential differences in measurement produced by different observers, and reducing the chances of isolated office hypertension. Nurse-recorded clinic BP values have recently been demonstrated to correlate equally as well with LVM as ambulatory BP (Nystrom et al 2005). Moreover, our group have recently demonstrated that on-treatment changes in LVM are as closely correlated with nurse-recorded conventional BP as ambulatory BP in newly diagnosed hypertensives of African origins (Skudicky et al 2002, chapter 5).

The clinical relevance of the present study relates to identifying a potential explanation for the conventional-BP independent increase in LVM that appears to exist in groups of African descent as compared to other ethnic groups (Skelton et al 2003, Lorber et al 2003, Kizer et al 2004, Rodriguez et al 2004, Drazner et al 2005), a change that may translate into a higher prevalence of CVD. In this regard, the present study supports the notion that nocturnal BP may account for a significant proportion of the variability in LVM index beyond conventional BP in men, but not in women.

The limitations of the present study include the fact that this is a cross-sectional and not a prospective study. Additional prospective analysis is presently underway. Further, the smaller study sample of men as compared to women could have limited the outcomes in men. In this regard, although in men nocturnal BP was associated with LVM index independent of conventional BP, I could not demonstrate a statistically significant difference between nocturnal BP and LVM index and conventional BP and LVM index relations. Furthermore, I could not demonstrate a statistically significant difference between nocturnal BP and LVM index and daytime BP and LVM index relations in this gender group.

In conclusion, the results of this first large study assessing the impact of diurnal variations in BP on LVM in groups of African descent suggest that in the general population, indexes of nocturnal decreases in BP are not associated with LVM index; daytime BP is as closely associated with LVM index as is nocturnal BP; conventional BP is as closely associated with LVM index as 24-hour, daytime and night-time BP, and ambulatory BP is not associated with LVM index independent of conventional BP. However, night-time BP may be associated with LVM index independent of conventional BP in men, but not in women. The mechanisms of this gender-specific effect of nocturnal BP on LVM index require further investigation.

Chapter 4

Blood Pressure-Independent Relationship Between Arterial Stiffness and Left Ventricular Mass in Subjects of African Ancestry.

ABSTRACT

As compared to Caucasians, groups of African as compared to European ancestry have an increased arterial stiffness, a change that may impact on central rather than peripheral (brachial artery) blood pressures (BP). In groups of European descent it is uncertain whether indices of arterial stiffness predict left ventricular mass index (LVMI) beyond blood pressure (BP). I therefore determined whether the relationship between an index of arterial stiffness (pulse wave velocity [PWV]) or wave reflection (central augmentation index [AIc]) and LVM is independent of conventional BP in randomly recruited subjects of African ancestry (n=399). Applanation tonometry was performed at the carotid, radial and femoral arteries and AIc and aortic PWV derived from these measures. LVM indexed for body surface area (LVMI) was determined using echocardiography. Univariate analysis demonstrated a relationship between PWV and LVMI ($r=0.28$, $p<0.0001$) and between AIc and LVMI ($r=0.19$, $p<0.001$), but on sex-specific analysis, the relationship between PWV and LVMI was present in women ($r=0.49$, $p<0.0001$), but not in men ($r=0.06$, $p=0.54$), whereas the relationship between AIc and LVMI was noted in both gender groups. After adjusting for age, body mass index, antihypertensive treatment, the presence or absence of diabetes mellitus or abnormal blood glucose control (HbA1c), non-independence of family members and either conventional systolic BP or pulse pressure, PWV ($r=0.25$, $p<0.0005$), but not AIc ($p=0.40$-0.86) was independently associated with LVMI in females. In males, neither PWV nor AIc were associated with LVMI independent of conventional BP and other confounders. In conclusion, PWV may refine the ability to predict LVMI beyond conventional BP in groups of African descent, but this effect is sex-specific being limited to females only.

4.1 INTRODUCTION

As indicated in chapter one of the present thesis, groups of African ancestry have a higher LVM than groups of European descent, changes that are independent of conventional BP (Skelton et al 2003, Lorber et al 2003, Kizer et al 2004, Rodriguez et al 2004, Drazner et al 2005, chapter 2). As LVM is a strong independent predictor of CVD (Casale et al 1986; Levy et al 1990; Koren et al 1991; Levy et al 1994; Verdecchia et al 1996; Ghali et al 1998; Devereux et al 2004[2]; Okin et al 2004), these ethnic differences could translate into a greater prevalence of CVD in groups of African descent. Therefore, it is particularly important to identify the determinants of LVM in groups of African ancestry. In this regard, the exact mechanisms responsible for an increased LVM in groups of African ancestry have not been identified. In chapter three I provide evidence to suggest that in men, a relationship between nocturnal, but not daytime BP and LVM index may in-part contribute toward a conventional BP-independent increase in LVM index. However, further factors need to be identified to account for conventional BP-independent changes in LVM index in groups of African ancestry, particularly in women.

Importantly, arterial stiffness appears to be higher in people of African ancestry as compared to Caucasians (Din-Dzietham et al 2004; Shiburi et al 2006; Chaturvedi et al 2004) and arterial stiffness is associated with LVM (Tatchum–Talom et al 1995; Kobayashi et al 1996; Bouthier et al 1985; Boutouyrie et al 1995; Roman et al 1996; Chen et al 1998; Roman et al 2000; Baguet et al 2000; Iketani et al 2000; Deague et al 2001, Gates et al 2003; Lekakis et al 2004). The impact of arterial stiffness on LVM may be independent of either conventional or ambulatory BP measured at the brachial artery as an increased arterial stiffness produces early reflected waves which influence central aortic pressures, a pressure that is not accurately measured by brachial artery BP measurements (Karamanoglu et al 1993, Williams et al 2006). However, few studies (Lekakis et al 2004, Leoncini et al 2006) have demonstrated a BP-independent relationship between indices of arterial stiffness and LVMI, with one study involving only a

small study sample (Lekakis et al 2004), and the other utilising the less well understood ambulatory arterial stiffness index (Leoncini et al 2006). In contrast, the majority of studies have failed to demonstrate a conventional BP-independent relationship between indices of arterial stiffness index and LVMI (Bouthier et al 1985; Boutouyrie et al 1995; Roman et al 1996; Chen et al 1998; Roman et al 2000; Baguet et al 2000; Iketani et al 2000; Deague et al 2001, Gates et al 2003). No studies have evaluated the BP-independent relationship between arterial stiffness and LVMI in either sex-specific groups or in groups of African descent. I therefore aimed to determine whether LVM is associated with indices of arterial stiffness and wave reflection independent of conventional BP in a relatively large, randomly selected population sample of African descent previously demonstrated by our group to have thresholds for arterial stiffness that exceed those of population groups of European descent (Shiburi et al 2006).

4.2 METHODS

Selection of the study group, the questionnaire data obtained, the anthropometric assessments and blood analysis, the conventional BP data obtained, and the echocardiographic assessments have been described in chapter 2. Of the 399 participants with high quality echocardiograms, PWV could not be measured in 72 subjects, because they had a bradycardia or were too obese.

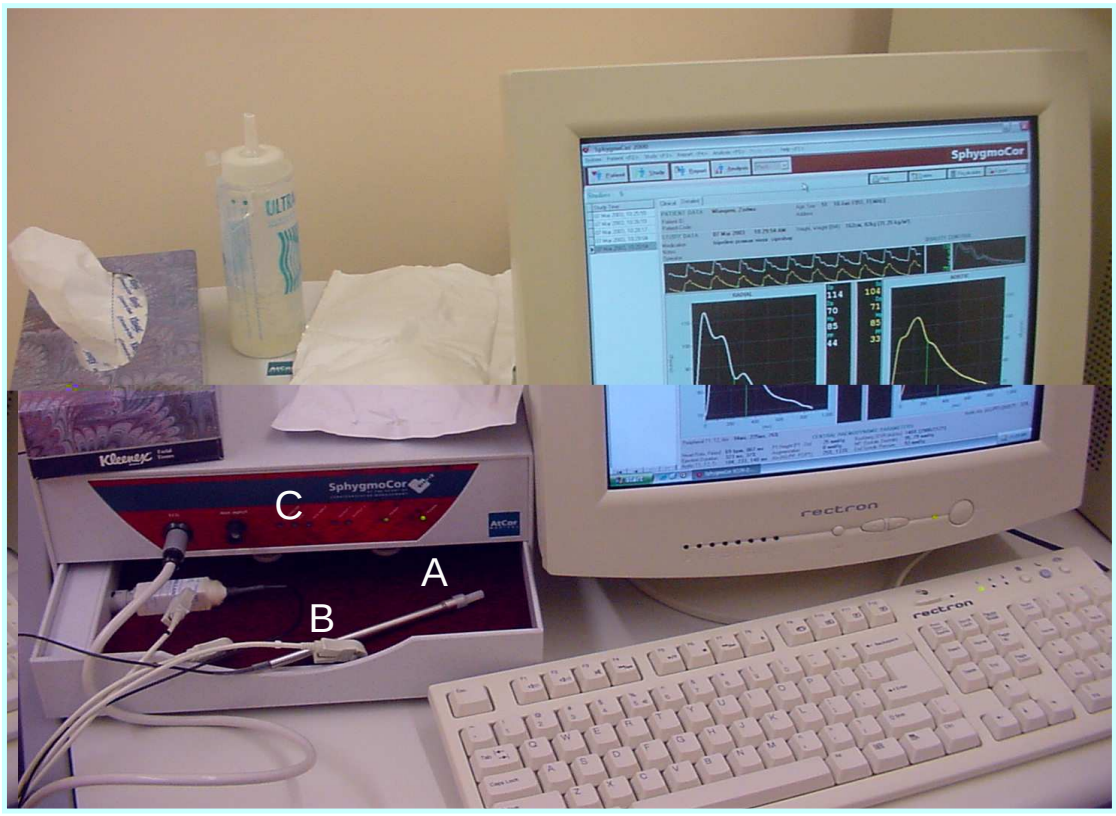
4.2.1 Pulse wave analysis.

Pulse wave velocity and AI were measured as previously described (Nichols and O'Rourke 1998). After subjects rested for 15 minutes in the supine position, the radial waveform was recorded at the dominant arm by applanation tonometry during an 8-second period. A high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston,

Texas), interfaced with a computer running the SphygmoCor software, version 6.21 (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia) was used to determine PWV and AI (Figure 4.1). Recordings (Figure 4.2) were discarded when the systolic or diastolic variability of consecutive waveforms exceeded 5%, or when the amplitude of the pulse wave signal was less than 80 mV. The pulse wave was calibrated by auscultatory measurement of the brachial BP immediately before the recordings. From the radial signal the SphygmoCor software calculates the aortic pulse wave by means of a validated (Nichols and O'Rourke 1998) generalized transfer function. The aortic (central arterial) AI(AIc) and peripheral AI were determined as the difference between the second and the first systolic shoulder (Figure 4.2) given as a percentage of the aortic pulse pressure. Aortic PWV was measured by sequential recordings of the arterial pressure waveform at the carotid and the femoral arteries. Distances from the suprasternal notch to the carotid sampling site (distance A) and from the suprasternal notch to the femoral artery (distance B) were measured. Pulse wave velocity distance was calculated as distance B minus distance A. Pulse transit time, calculated as the mean time difference between sites A and B (Figure 4.2) was determined from the average of 10 consecutive beats. Aortic PWV was calculated as the ratio of the distance in meters to the transit time in seconds.

4.2.3 Statistical Analysis.

The software and the database management for this study have been described in chapter 2. Means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. Linear regression analysis was used to determine the relationships between BP, PWV and AI with LVMI. Regression relations were adjusted for age, gender, BMI, antihypertensive treatment, the presence or absence of diabetes mellitus/impaired blood glucose control (HbA1c>7.0%) and either systolic BP or pulse



A Applanation tonometer

B ECG electrodes

C SphygmoCor device

Figure 4.1 Illustrates the hardware used to determine pulse wave velocity and augmentation index.

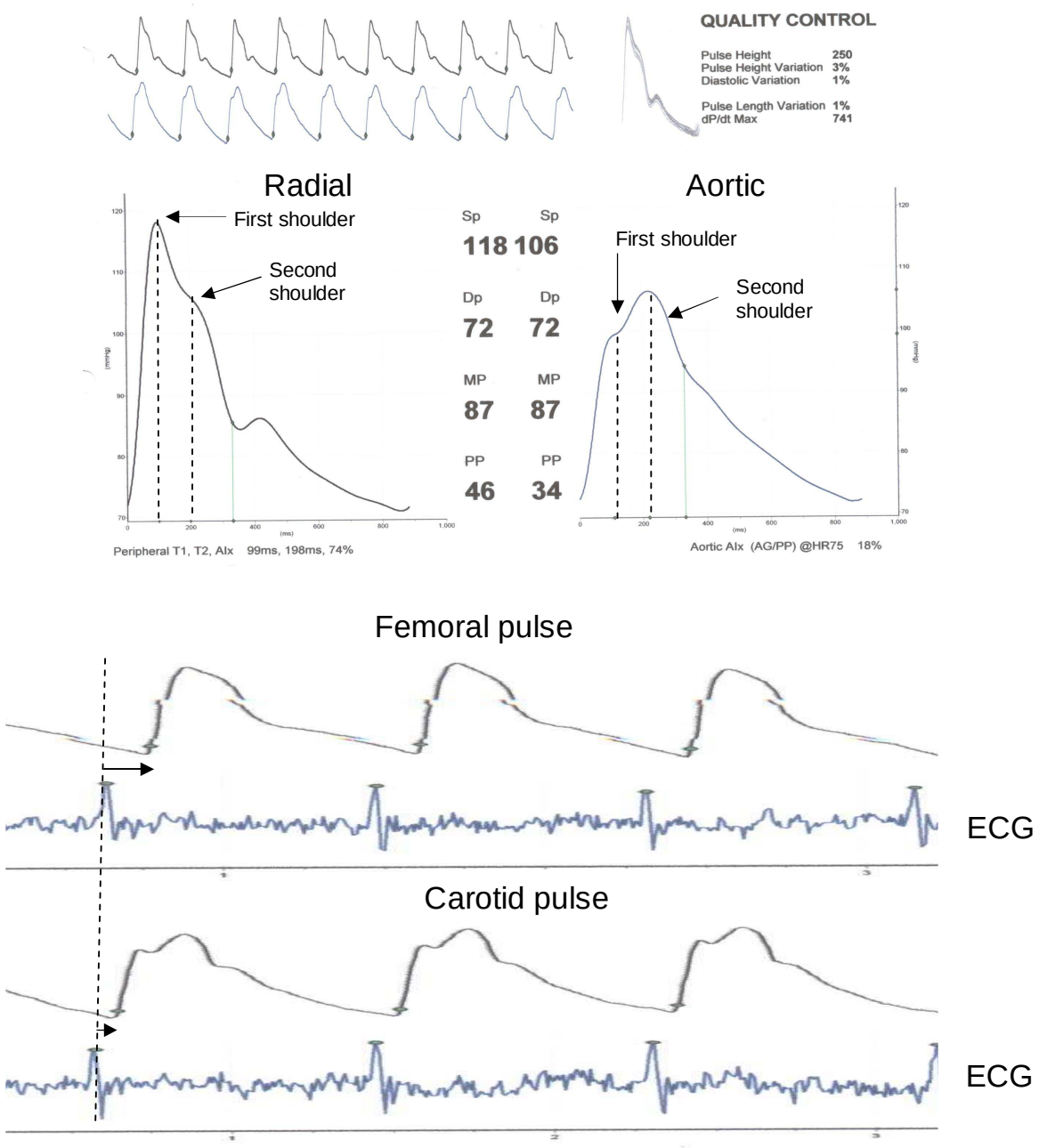


Figure 4.2. Illustrates an example of the applanation tonometry recordings obtained t determine augmentation index (AI) (upper panel) and pulse wave velocity (PWV)(lower panel). The figures in the upper panel show pulse waves obtained from the femoral and carotid artery indicating the points (first and second shoulders) from which augmentation index is derived. The arrows in the lower panel indicate the time differences between electrical events and the arterial pressure changes in the carotid and femoral arteries used to calculate PWV. See text for a further description.

pressure. For statistical analysis of the relations and the derivation of probability values, further adjustments were made for non-independence of family members. Sensitivity analysis was conducted in participants not receiving antihypertensive therapy and in sex-specific groups.

4.3 RESULTS

4.3.1 Characteristics of the participants.

Table 4.1 gives the demographic and clinical characteristics of the study group. More women than men participated. In general the group had a high BMI and 66% of participants were either overweight or obese. The increased adiposity was especially prevalent in women. More men than women smoked and reported intake of alcoholic beverages. More women than men were receiving antihypertensive medication at the time of the study, but a similar proportion had no previous history of receiving such medication (81.9 versus 77.4%; p=0.39).

Table 4.1 also gives the central and peripheral haemodynamic values of the study group. Apart from heart rate which was lower in men, there were no gender differences in central and peripheral haemodynamic values.

Table 4.2 lists the echocardiographic measurements. Men had larger LV dimensions and a greater LVM and LVM index than women.

4.3.2 Association between indices of arterial stiffness/wave reflection and blood pressure.

PWV and AIc were correlated with each other (r=0.30, p<0.0001). Importantly, both PWV (r=0.64, p<0.0001) and AIc (r=0.43, p<0.0001) were strongly correlated with

Table 4.1. Demographic, anthropometric, and clinical characteristics.

	All subjects	Women	Men
Number	327	204	123
Age (years)	43.1 ± 18.4	42.8 ± 18.0	43.5 ± 19.0
BMI (kg/m^2)	28.5± 6.8	30.3± 7.0	25.4± 5.1**
% overweight/obese	28/38	25/49	32/20**
Regular tobacco intake (% subjects)	13	3	30**
Regular alcohol intake (% subjects)	22	14	36**
% with DM or with an HbA1c>7.0%	9	8	10
HbA_{1C} (%)	6.08±1.2	6.07±1.09	6.11±1.41
% with hypertension	41	43	40
Current antihypertensive medication (%)	23	28	14*
Conventional SBP/DBP (mm Hg)	130±22/84±12	129±23/83±12	132±21/85±12
Pulse pressure (mm Hg)	46±15	45±15	48±15
Peripheral augmentation index (%)	84±22	85±24	81±20
Central augmentation index (%)	27±14	27±14	26±13
Aortic pulse wave velocity (m/sec)	6.82±3.23	6.76±3.18	6.92±3.34
Pulse rate (beats/min)	68±10	71±10	64±9**

BMI, body mass index; DM, diabetes mellitus; HbA_{1C}, glycosylated hemoglobin; SBP/DBP, systolic blood pressure/diastolic blood pressure. *p<0.05 , ** p<0.001 versus women.

Table 4.2. Echocardiographic characteristics.

	All subjects	Women	Men
Sample number	327	204	123
LV end diastolic diameter (cm)	4.74±0.49	4.61±0.46	4.94±0.48**
LV septal wall thickness (cm)	1.02±0.17	1.00±0.16	1.05±0.18*
LV posterior wall thickness (cm)	0.98±0.15	0.96±0.14	1.01±0.16*
LV mean wall thickness (cm)	1.00±0.16	0.98±0.15	1.03±0.16*
LV mass (g)	170±51	159±43	189±56**
LV mass index (g/m^2)	96±25	90±22	104±27**

LV, left ventricle; * p <0.01, ** p<0.001 versus women.

conventional systolic BP (Figure 4.3). Similarly, both PWV (r=0.62, p<0.0001) and AIc (r=0.35, p<0.0001) were strongly correlated with conventional pulse pressure.

4.3.3 Association between blood pressure and LVMI.

Consistent with data shown in chapter 3, after adjustments for age, gender, BMI, antihypertensive treatment, the presence or absence of diabetes mellitus or abnormal blood glucose control and for non-independence of family members; conventional systolic BP (r=0.23, p<0.0001) and pulse pressure (r=0.27, p<0.0001), but not diastolic BP were associated with LVMI.

4.3.4 Association between indexes of arterial stiffness/wave reflection and LVMI.

On univariate analysis PWV was correlated with LVMI (Figure 4.4). Furthermore, both central and peripheral AI were correlated with LVMI (AIc, r=0.19, p=0.0006; AIp, r=0.19, p=0.0007). On univariate analysis PWV was correlated with LVMI in women, but not in men (Figure 4.4). In contrast, AIc and AIp were correlated with LVMI in both men (AIc; r=0.24, p=0.008, AIp; r=0.26, p=0.004) and in women (AIc; r=0.20, p=0.004, AIp; r=0.20, p=0.004).

After adjustments for age, BMI, antihypertensive treatment, the presence or absence of diabetes mellitus/impaired blood glucose control (HbA1c>7.0%), non-independence of family members and either systolic BP or pulse pressure, PWV was associated with LVMI in women, but not in men (Figure 4.5). On sensitivity analysis, a strong and independent relationship between PWV and LVMI was similarly noted in untreated women, but not in untreated men (Figure 4.5). However, neither central (r=-0.06, p=0.40) nor peripheral (r=-0.03, p=0.67) AI were associated with LVMI after adjustments for conventional systolic BP and other confounders in women. However, a modest, and independent relationship between central (r=0.20, p=0.012) or peripheral

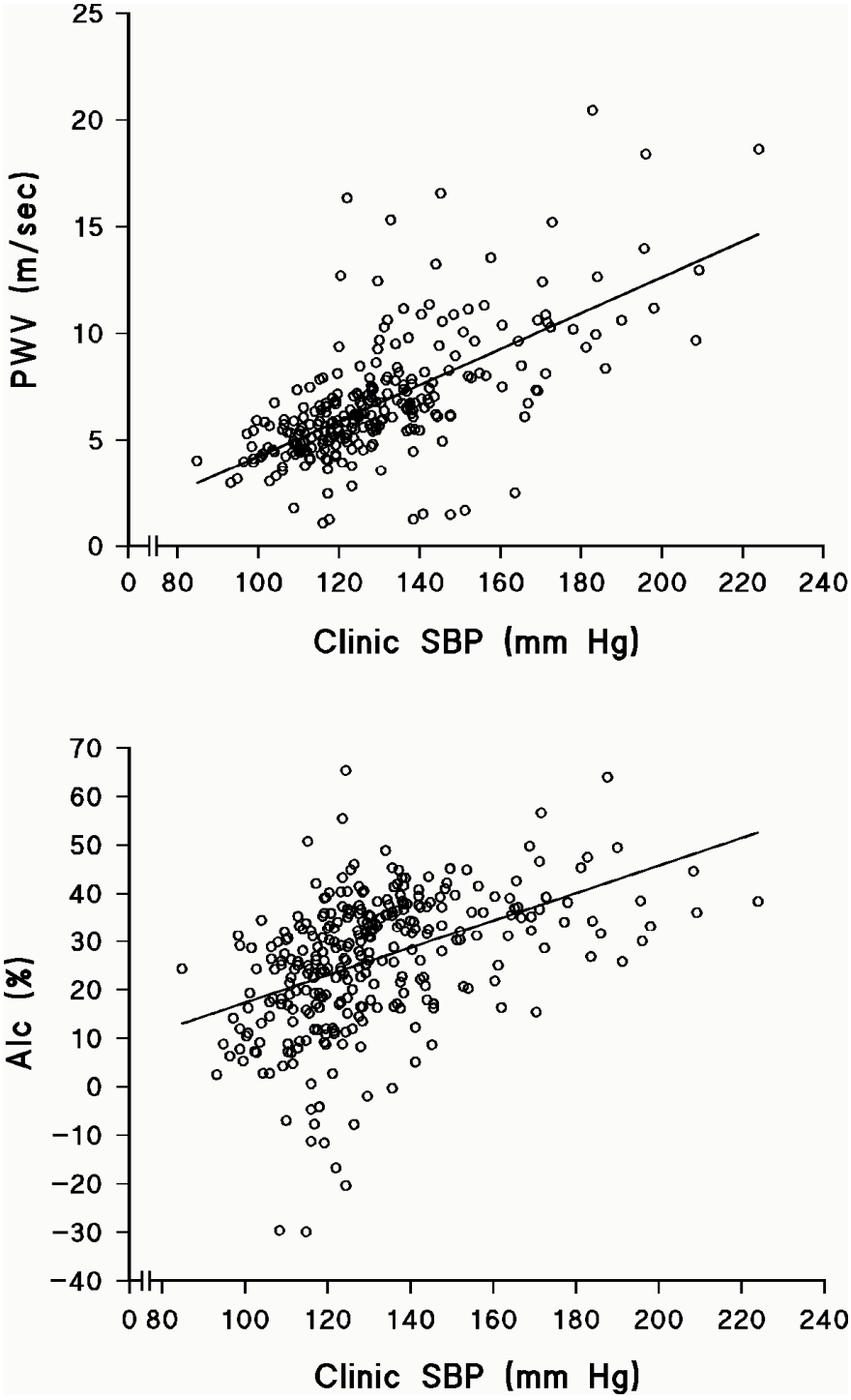


Figure 4.3. Relationships between indexes of arterial stiffness and conventional systolic blood pressure (SBP). PWV, pulse wave velocity; AIc, central or aortic augmentation index. See text for regression coefficients.

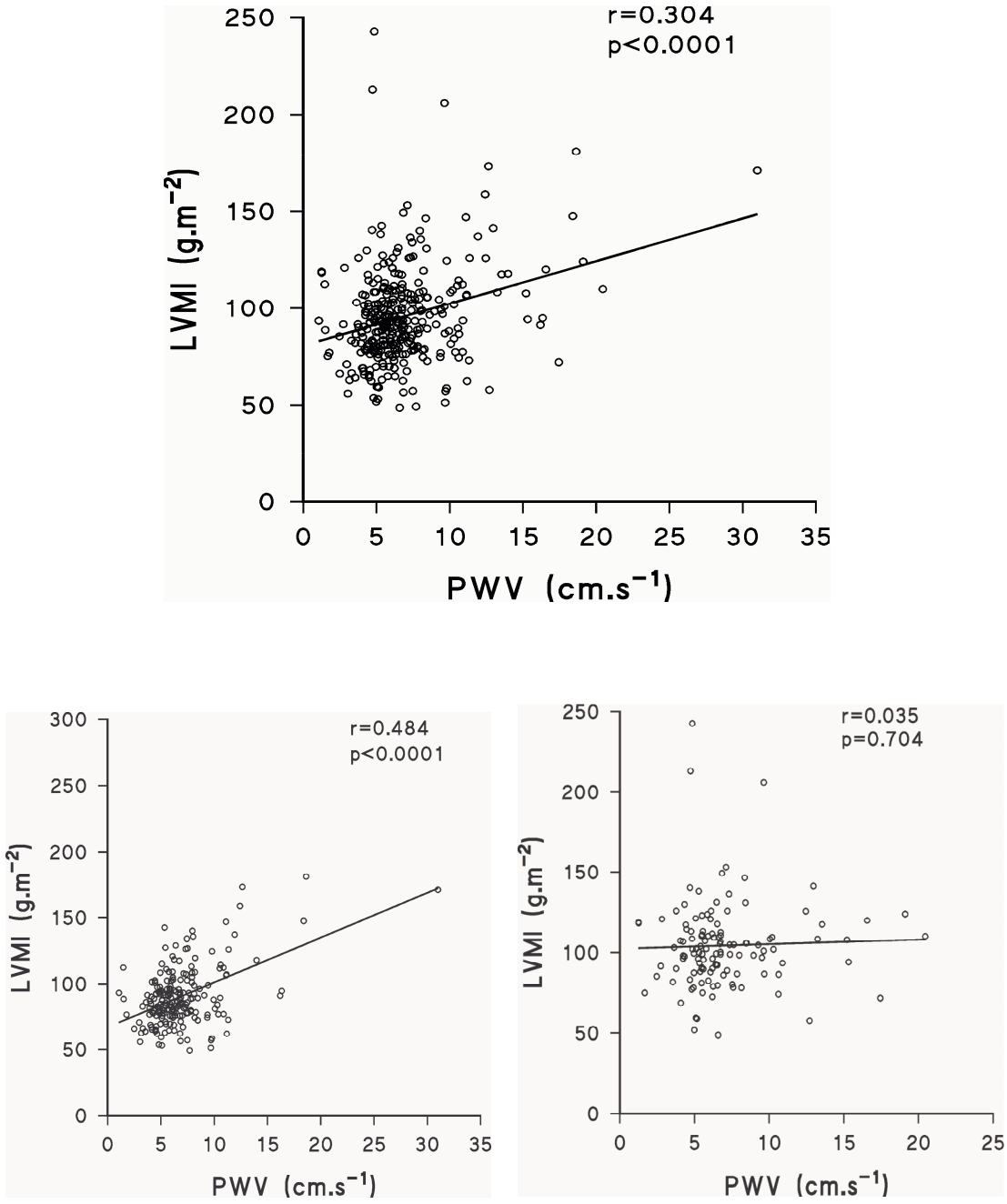


Figure 4.4. Relationship between pulse wave velocity (PWV) and left ventricular mass index (LVMI) in study subjects. The upper panel illustrates the relationship in all subjects and the lower panel the relationships in women (left panel) and men (right panel).

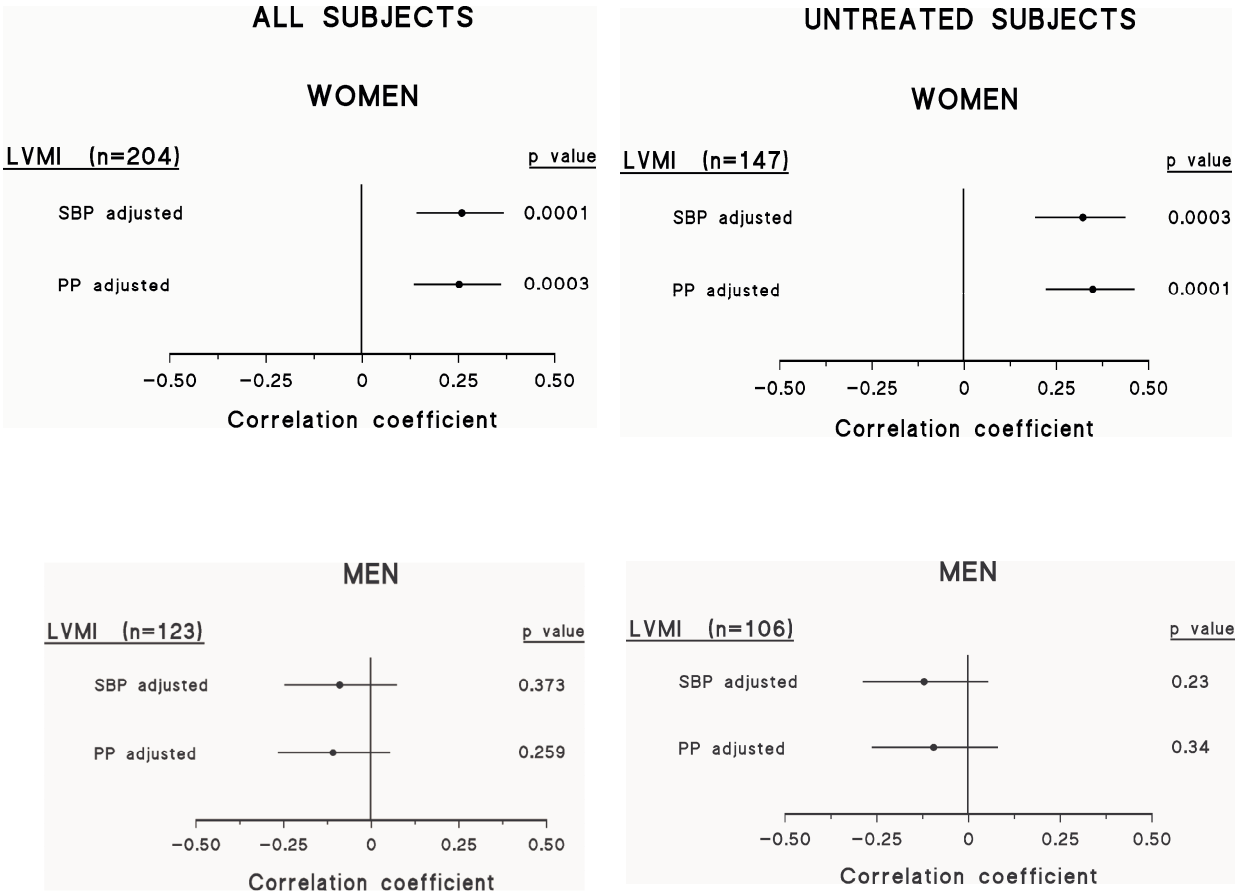


Figure 4.5. Blood pressure (BP)-independent relations between pulse wave velocity (PWV) and left ventricular mass index (LVMI) in sex-specific groups. Correlation coefficients (partial r) and 95% confidence intervals (CI) for the relations are shown in all subjects and in subjects not receiving antihypertensive therapy. SBP, systolic BP; PP, pulse pressure. Partial r values were obtained after adjustments for age, BMI, antihypertensive treatment (in all subjects), the presence or absence of diabetes mellitus or abnormal blood glucose control and either SBP or PP. Probability values were obtained with an additional adjustment for non-independence of family members.

(r=0.20, p<0.02) AI and LVMI was noted in men, an effect that was nevertheless absent in untreated subjects.

4.3 DISCUSSION

The main finding of the present study is that in a relatively large, randomly selected population sample of African descent with a high prevalence of excess adiposity (~65%) and both treated (~23%) and untreated (~18%) hypertension, PWV was associated with LVM index independent of conventional BP and other confounders in women, but not in men. This effect was reproduced in untreated subjects.

The present results provide the first evidence at a population level that in groups of African descent an index of arterial stiffness provides information beyond that of peripheral brachial BP measurements when predicting LVM index. The outcome of the present study is consistent with two studies conducted in groups of European ancestry (Lekakis et al 2004, Leoncini et al 2006) demonstrating the importance of a measure of arterial stiffness as a brachial artery BP-independent predictor of LVM. However, one of these studies (Lekakis et al 2004) involved only 48 hypertensive patients. Moreover, in the other study (Leoncini et al 2006) the less well established ambulatory arterial stiffness index was employed as a measure of arterial stiffness. In this regard, the extent to which the information derived from the ambulatory arterial stiffness index is comparable with that of pulse wave analysis is uncertain as the correlation coefficient between the two is ~0.5 (Li et al 2006).

The outcome of the present study is in contrast to previous studies (Bouthier et al 1985; Roman et al 1996; Chen et al 1998; Roman et al 2000; Baguet et al 2000; Deague et al 2001) that have observed no additional predictive power of measures of arterial stiffness in relation to LVM beyond that provided by conventional BP measurements in groups of European ancestry. Two studies conducted in groups of European ancestry (Bouthier et al 1985, Baguet et al 2000) in which PWV was used as an index of arterial

stiffness, included only a small sample of hypertensive patients. In these studies (Bouthier et al 1985, Baguet et al 2000), insufficient sample sizes and a narrow range of BP values only encompassing the upper tail of the distribution in the population at large might have reduced the power of previous studies to detect an independent association between LVM index and PWV. One large population-based study failed to show a BP-independent effect of PWV on LVM index (Deague et al 2001), but no gender-specific analysis was conducted. In this regard, in the present study we noted a marked gender-specific effect of PWV on LVM index. Other previous studies conducted in groups presumably of European descent with large sample sizes that have failed to demonstrate a BP-independent effect of indices of arterial stiffness on LVM (Roman et al 1996; Chen et al 1998; Roman et al 2000) have employed different measurements to derive indices of arterial stiffness. Whether the information derived from other indices is comparable with that of pulse wave analysis is uncertain.

In the present study, although PWV was associated with LVM index independent of BP, AI was not, confirming that AI and PWV cannot be used as surrogates of each other (Lemogoum et al 2004). The lack of BP-independent effect of central AI on LVM index is consistent with previous studies (Deague et al 2001). There are a number of potential explanations for the contrasting effects of PWV and AI on LVM index. These might relate to the dependence of central AI, but not PWV, on ventricular ejection time and heart rate (Wilkinson et al 2002). Further, unlike PWV, AI also depends on the distance of the reflection points to the heart. It is possible that in a large population sample, subjects with a higher PWV might have reflection points further from the heart.

The strengths and potential limitations of the present study should be underscored. The strong points of the study are the population-based approach, the relatively large sample size, and the use of conventional BP measurements that have previously been demonstrated to be as closely correlated with LVM index as ambulatory BP values (see chapter 3). The limitations are the cross-sectional, rather than longitudinal nature of the study design, and the relatively small sample size for men (n=123) as

compared to women (n=204). However, the BP-independent relationship between PWV and LVM index in women was robust (partial r=0.26, p<0.0001), whilst no relationship was noted in men (partial r=-0.09, p=0.37). Moreover, on sensitivity analysis conducted in untreated subjects, the outcomes were similarly robust (r=0.32, p=0.0003 for women and r=-0.12, p=0.37 for men). Hence, it is unlikely that increasing the sample size for men would alter the outcomes of this study.

In conclusion, the present study suggests that measures of arterial stiffness offer information beyond that of conventional BP measured at the brachial artery when predicting LVM index in a group of African descent, albeit that this effect is gender-specific.

Chapter 5

Relationship between Treatment-induced Changes in Left Ventricular Mass and Ambulatory Versus Conventional Blood Pressure in Hypertensive Patients of African Descent.

ABSTRACT

There is substantial controversy as to whether conventional, daytime or nocturnal BP best predicts the regression of LVM. Studies that have been conducted to-date have been exclusively performed in groups of European descent. However, as groups of African descent have an attenuated nocturnal decline in BP, antihypertensive-induced decreases in LVM may depend more on changes in ambulatory than on conventional BP in this ethnic group. In a single-center study, the extent to which changes in conventional and ambulatory BP predicted regression of LVM index in response to antihypertensive treatment in previously untreated and treated patients of African ancestry with sustained hypertension was explored. In this study 173 patients who, off treatment, had a daytime diastolic BP ranging from 90 to 114 mm Hg were enrolled. Antihypertensive drugs were titrated and combined to reduce the daytime diastolic BP below 90 mm Hg. Echocardiograms were obtained at baseline and follow-up. Mean systolic/diastolic clinic BP, 24-hour BP, and LVM index were similar in previously untreated (n=64) and previously treated (n=109) patients and averaged 171/102 mm Hg, 151/97 mm Hg, and 118 g/m^2, respectively. At 4 months, these values had decreased ($P<0.001$) by 26/12 mm Hg, 23/14 mm Hg, and 14 g/m^2 in previously untreated patients and by 22/9 mm Hg, 21/13 mm Hg, and 19 g/m^2 in previously treated patients. In the previously untreated patients, the regression in LVM index correlated to a similar degree ($p<0.09$) with the decreases in the conventional ($r=0.34$; $p<0.005$) and the 24-hour ($r=0.26$; $p<0.04$) systolic BP. In the previously treated patients, the corresponding correlations were 0.02 ($p<0.82$) and =0.10 ($p<0.32$), respectively. Compared with the 24-hour systolic BP, automated oscillometric measurements of systolic BP obtained at the clinic yielded similar results. Thus, in previously untreated patients of African ancestry with sustained hypertension followed at a single center, reductions in clinic and ambulatory systolic pressure in response to antihypertensive treatment equally predicted the regression in LVM index.

5.1 INTRODUCTION

As indicated in chapters 1 and 2, LVM is a strong independent predictor of CVD (Casale et al 1986; Levy et al 1990; Koren et al 1991; Levy et al 1994; Verdecchia et al 1996; Ghali et al 1998; Devereux et al 2004[2]; Okin et al 2004). Recent studies (Fagard et al 1997[3] and Fagard et al 2000) and three meta-analyses (Schlaich et al 1998, Dahlof et al 1992, Jennings and Wong 1997) on antihypertensive treatment have demonstrated that reductions in LVM correlate with decreases in BP. However, controversy still exists with regard to the type of BP measurement (conventional, automated, or ambulatory) that best correlates with changes in LVM induced by antihypertensive treatment (reviewed by Fagard et al 1997[3]).

Some studies have indicated that ambulatory BP is more closely associated with the regression of LVH in hypertension (reviewed by Fagard et al 1997[3]). In most previous studies the investigators did not exclude previously treated or white-coat hypertensive patients. With respect to white coat hypertension, in older patients with isolated systolic hypertension, active treatment compared with placebo reduced electrocardiographic voltages only in patients with sustained hypertension and not in those with white-coat hypertension (Fagard et al 2000). Moreover, previous studies were multi-centre studies, thus increasing the difficulty in standardizing clinic measurements of BP. Further, all previous studies assessing the relationship between on-treatment decreases in BP and LVM have been conducted in groups of European descent (reviewed by Fagard et al 1997[3]). As groups of African descent have an attenuated nocturnal decline in BP (Profant and Dimsdale 1999, Wang et al 2006), this raises the question of the relevance of the outcomes of previous studies to groups of African descent? In groups of African descent, ambulatory BP is unable to predict LVM index beyond conventional BP, except perhaps in men (chapter 3). Whether antihypertensive-induced decreases in LVM may depend more on ambulatory than on conventional BP in groups of African ancestry requires further study.

The Baragwanath Hypertension Study was a single-center, randomized trial that compared several drug classes to initiate treatment in patients of African ancestry with sustained hypertension confirmed by ambulatory BP monitoring (Sareli et al 2001). In the present analysis, to what extent changes in conventional and automated BP readings at the clinic and in the ambulatory BP, predict regression of LVM index in response to antihypertensive treatment in previously untreated or treated patients with sustained hypertension was assessed.

5.2 METHODS

5.2.1 Subjects and Procedures

The Baragwanath Hypertension Study was a single-center, randomized, open-label trial conducted at the Chris Hani-Baragwanath Hospital from 1994 through 1997. Men and women of African descent were enrolled if they were 18 to 70 years of age and free of clinically significant cardiovascular or noncardiovascular disorders. Women of reproductive age had to use adequate contraception. All patients gave informed written consent.

Patients diagnosed as being hypertensive after a 2-week placebo run-in period and with a count of returned placebo tablets within 80% to 120% of the expected number qualified for randomization if, in addition, their daytime diastolic BP was 90 to 114 mm Hg. Eligible patients were randomized to nifedipine gastrointestinal therapeutic system (GITS) 30 mg/d, verapamil slow release (SR240 mg/d, hydrochlorothiazide 12.5 mg/d, or enalapril 10 mg/d (Sareli et al 2001). Patients were followed up at monthly intervals. The target BP was a daytime diastolic pressure of <90 mm Hg. If at the first monthly follow-up visit the target was not reached, the daily dose of the first-line drug was increased, as follows: nifedipine GITS to 60 mg, verapamil SR to 360 mg, hydrochlorothiazide to 25 mg, and enalapril to 20 mg. At 2 months, patients of the nifedipine GITS group who had not

achieved the target BP were additionally randomized to 1 of the following 4 treatment strategies: the addition of enalapril (10 mg/d), carvedilol (25 mg/d), or verapamil SR (120 mg/d) or increasing the daily dose of nifedipine GITS to 90 mg. In the uncontrolled patients of the verapamil SR group, the daily dose of the calcium-channel blocker could be increased to 480 mg. Patients not controlled on hydrochlorothiazide 25 mg/d received reserpine 0.125 mg/d, and those not controlled on enalapril 20 mg/d were given hydrochlorothiazide 12.5 mg/d.

All patients randomized in the Baragwanath Trial underwent echocardiography at baseline. However, only patients in whom high-quality echocardiograms could be obtained were eligible for inclusion in the echocardiographic substudy.

5.2.2 Blood pressure measurements

At baseline and at each of four follow-up visits, BP was assessed with three techniques. First, after the patient had rested in the sitting position for 10 minutes, the study nurse measured the conventional BP three times consecutively according to the recommendations of the American Heart Association (Frohlich et al 1998). The same nurse performed the conventional BP readings in all patients. Subsequently, the sitting BP was recorded ten times consecutively at three-minute intervals using calibrated Dinamap 1846 SX oscillometric monitors (Critikon Inc) (Borrow et al 1982). For analysis, the three conventional and ten Dinamap automated BP measurements were averaged.

Furthermore, oscillometric SpaceLabs 90207 devices (O'Brien et al 1991) (SpaceLabs Inc) were programmed to obtain BP readings every fifteen minutes from 6:00 AM to 10:00 PM and every thirty minutes from 10:00 PM to 6:00 AM. The intraindividual BP means were weighted by the time interval between successive BP readings. For analysis, the daytime period was defined as the time interval from 6:00 AM to 6:00 PM and nighttime ranged from 10:00 PM to 4:00 AM. Previous studies in hypertensive patients of African descent have shown that this definition excludes the rapid BP changes

in the morning and evening (Sareli et al 2001).

5.2.3 Echocardiography

At randomization and at 4 months, M-mode, 2-dimensional, pulse and color Doppler echocardiograms were obtained with a Hewlett-Packard Sonos 2500 system using a 2.5-MHz transducer as described in chapter 2. Briefly, M-mode echocardiography of the left ventricle was performed in the short-axis view. M-mode variables were analyzed according to the American Society of Echocardiography Convention (Sahn et al 1978) and included left ventricular end-diastolic and end-systolic diameters and septal and posterior wall thickness. All measurements were recorded on videotape and analyzed by the same experienced echocardiographer who was unaware of the BP and the clinic data of the patients. For statistical analysis, measurements were averaged over three heart cycles. Doppler estimation of the stroke volume was assessed as previously described (Dubin et al 1990). LVM was adjusted for body size according to an anatomically validated regression method (Devereux et al 1986). Replicate measurements of LVM index showed that in the present study population, the interobserver and intraobserver coefficients of variation were 12.4% and 11.4%, respectively.

5.2.4 Statistical Analysis

Database management and statistical analysis were performed with SAS software, version 6.12 (SAS Institute Inc). Previously untreated and treated patients were compared using Student's t test and the X^2 statistic for continuous measurements and class variables, respectively. Single and stepwise multiple regression analyses were used to analyze the relationship between changes in LVM or LVM index and various

explanatory variables, including the treatment-induced BP changes. Multivariate ANOVA was performed to test the null hypothesis of no differences between the parameters of regression equations (SAS Institute Inc, 1987).

5.3 RESULTS

5.3.1 Demographic Characteristics

Of the 409 patients randomized in the trial, 233 (57%) were eligible for inclusion in the present substudy because echo-cardiograms of sufficient quality had been obtained. Of the latter patients, 23 (10%) had been withdrawn at 4 months and 37 (16%) did not have all measurements at baseline or at 4 months required for the statistical measurements. Thus, this study includes 173 patients who, compared with the 236 nonparticipants, had similar BP values at entry (Table 5.1). However, nonparticipants were older, more obese, and included slightly more previously treated patients (46% versus 37%, respectively, p=0.052)

The 173 patients (41 men and 132 women) were 51±10 years of age. Their body-mass index averaged 30.3±6.2 kg/m^2. Of the 173 patients, 109 had previously been treated, and 85 patients had been on monotherapy either with diuretics (n=48), angiotensin-converting enzyme inhibitors (n=20), α-methyldopa (n=9), or calcium channel blockers (n=8). Furthermore, 17 patients had been on multiple drugs, including diuretics in 11 patients, and 7 patients could not report which drug treatment they had been taking before the screening visit. Compared with the untreated patients, the previously treated patients included more women and had higher mean body-mass index (Table 5.1). At entry, clinic, Dinamap and ambulatory BP values (Table 5.2) as well as all echocardiographic measurements (Table 5.3) were similar in previously untreated and treated patients (p>0.04).

Table 5.1. Clinical Characteristics at Randomization of Participants and Nonparticipants

		Participants		
	Nonparticipants	Previously Untreated	Previuosly Treated	All Included
No	236	64	109	173
Age,y	55±10	49±11	52±9	51±10*
Female sex, n (%)	181 (77)	40 (62.5)	92 (84.4)‡	132 (76)
BMI (kg/m^2)	31.8±7	28.4±6	31.4±6‡	30.3±6.2†
Systolic/Diastolic BP (mm Hg)				
Conventional	173±18/103±7	170±17/103±9	172±21/102±9	172±21/102±9
Dinamap	166±18/99±8	162 ±16/100±7	165±21/100±8	165±21/100±8
24-Hour	150±15/96±7	149±15/96±7	153±15/97±7	153±15/97±7
Daytime	155±14/102±7	153±15/102±7	158±14/103±7	158±14/103±7
Nighttime	139±18/85±10	140± 18/86±10	143±20/87±11	143±20/87±11

Values are mean±SD.

*p<0.01 and †p=0.03, significance of the difference between participants and nonparticipants,

‡ p=0.002, significance of the difference betweenpreviuosly untrated and previously treated patients.

Table 5.2. Conventional, Dinamap, and Ambulatory BP at Baseline and at 4 Months.

BP, mm Hg	Baseline	4 Months	Change
Previously untreated (n=64)			
Conventional	170±17/103± 9	144±21/91±11	-26 ±25/-12±14
Dinamap	162±16/100±7	137±19/88±10	-25 ±21/-12±11
24-hour	149±15/96±7	126±14/92±18	-23 ±15/-14±9
Daytime	153±15/102±7	130±14/87±8	-23±16/-15±9
Nighttime	140±18/86±10	119±17/73±10	-21±16/-13±10
Previously treated (n=109)			
Conventional	172±21/102±9	150±22/93±11	-22±27/-9±14
Dinamap	165±21/100±8	143±20/90±11	-22±26/-10±12
24-hour	153±15/97±7	132±14/85±9	-21±17/-13±10
Daytime	158±14/103±7	135±15/90±10	-22±17/-13±10
Nighttime	143±20/87±11	124±17/75±10	-19±19/-12±12

All changes in blood pressure were significant ($p<0.001$)

Table 5.3. Echocardiographic Data at Baseline and at 4 Months.

Characteristic	Baseline	4 Months	Change	p-value
Previuosly untreated (n=64)				
LVEDD, mm	47.0±4.9	46.4±4.6	-0.6±5.1	0.34
PWT,mm	11.1±0.21	10.3±1.7	-0.7±2.1	0.007
IVS, mm	11.9±2.3	11.0±1.7	-0.9±2.2	0.003
MWT, mm	11.5±2.1	10.7±1.4	-0.8±1.9	0.001
LVM, g	205±55	181±40	-24.4±42.9	<0.001
LVMI, g/m^2	118±33	104±23	-14.3±26.1	<0.001
Stroke Volume, ml	73±16	74±18	0.099	0.32
Previuosly treated (n=109)				
LVEDD, mm	45.7±6.3	43.9±5.8	-1.8±6.4	0.004
PWT, mm	11.5±2.3	10.7±1.8	-0.8±2.3	<0.001
IVS, mm	12.6±2.0	11.6±1.9	-1.0±2.0	<0.001
MWT, mm	12.0±1.9	11.2±1.6	-0.9±1.8	<0.001
LVM, g	212±70	178±55	-33.7±52.6	<0.001
LVMI, g/m2	118±34	99±26.1	-18.6±29.1	<0.001
Stroke volume, ml	73±17	73±16	-0.00008	0.96

LVEDD: left ventricular end-diastolic diameter; PWT: posterior wall end-distolic thickness; IVS: interventricular septum end-diastolic thickness; and MWT: end-diastolic mean wall thickness

5.3.2 Results in Previously Untreated Patients

The number of patients who remained on monotherapy was 27 of 39 in the nifedipine group, 6 of 9 in the verapamil SR group, 2 of 8 in the enalapril group, and 4 of 8 in the hydrochlorothiazide group.

At 4 months, compared with baseline, BP measured at the clinic by the study nurse or by the Dinamap device had significantly ($p<0.001$) decreased (Table 5.2). In addition, there was a parallel shift ($p<0.001$) of the systolic and diastolic ambulatory BP profiles to lower values (Figure 5.1 and Table 5.2). The treatment-induced changes in the BP recorded oscillometrically, either at the clinic or over 24 hours, were significantly correlated with the correspondingchanges in the conventionally measured office readings (Figure 5.2).

After 4 months of antihypertensive therapy, LVM and LVM index had decreased ($p<0.001$) by 24 g and 14 g/m^2, respectively (Table 5.3). This was achieved through a reduction in wall thickness with no significant change in left ventricular end-diastolic diameter. Both before and after standardization for body surface area, there was a positive linear relationship between the decrease in LVM index and the reduction in systolic BP as assessed by conventional or automated measurement at the clinic or by 24-hourambulatory monitoring (Table 5.4). The corresponding relationship for diastolic pressure was not statistically significant (Table 5.4). Considering conventional, Dinamap, and 24-hour BP measurements, there were no significant differences in the regression parameters relating the changes in LVM to those in BP ($p\geq0.09$). These findings remained unaltered when LVM index was used as an outcome variable (Figures 5.3 and 5.4). In addition, measurement of the 24-hour or Dinamap BP did not significantly increase the accuracy of the prediction of the changes in LVM ($p>0.40$) or LVM index ($p>0.37$) over and beyond that already provided by conventional systolic pressure.

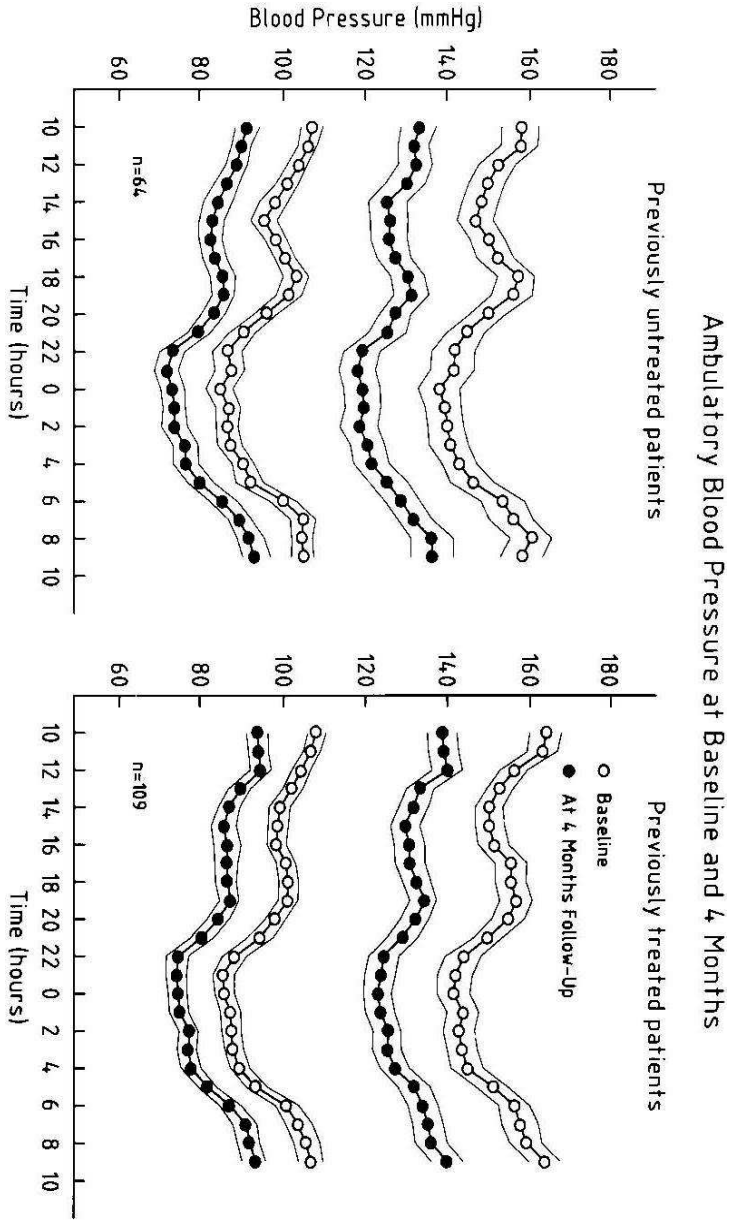


Figure 5.1. Systolic and diastolic blood pressure profiles (BP) at baseline (open symbols) and at 4 months of treatment (closed symbols) in hypertensive patients of African descent. Values are hourly BP means with 95% confidence intervals. Results are given separately for previously untreated and treated patients.

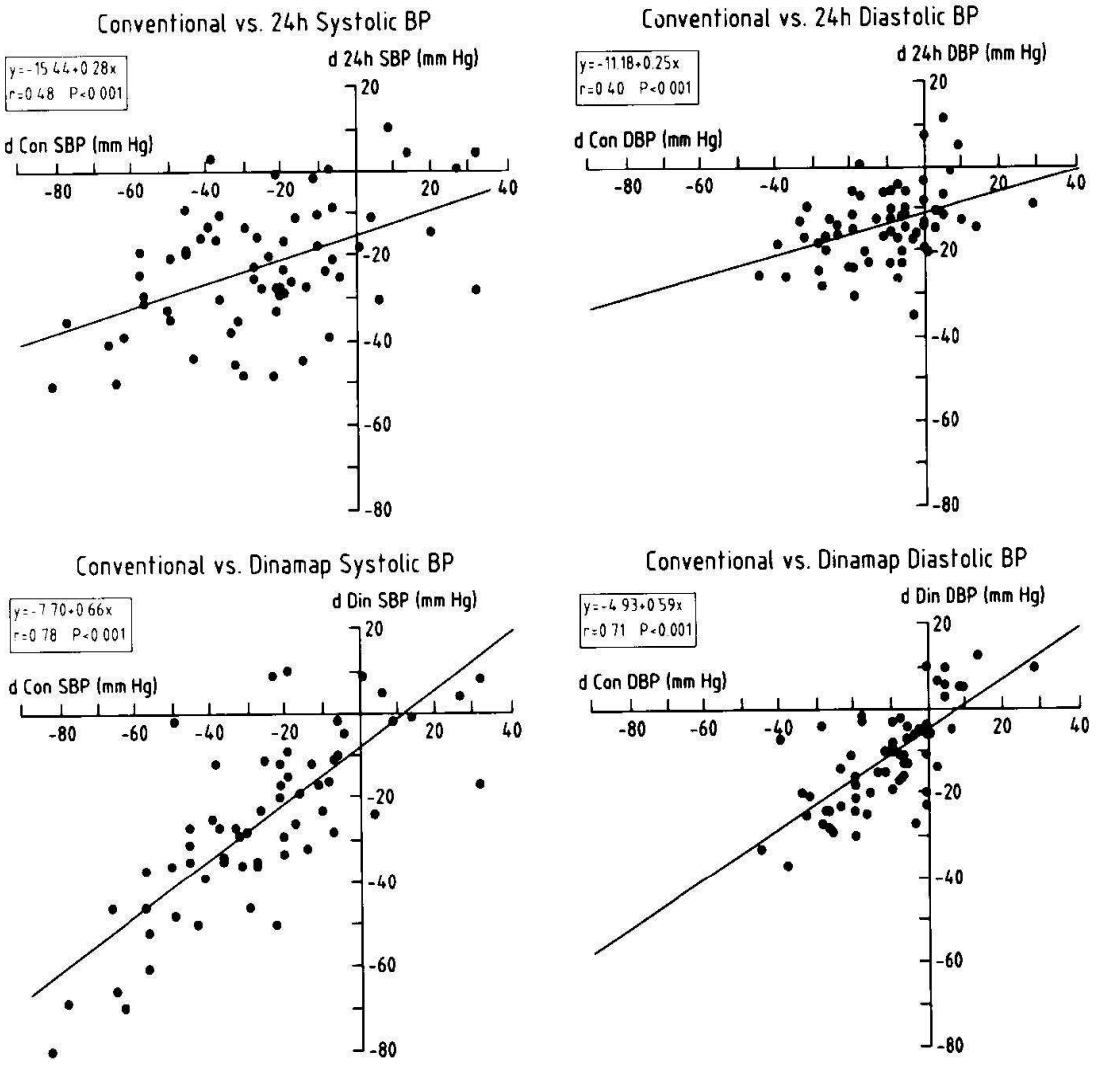


Figure 5.2. Relationships in previously untreated hypertensive patients of African descent between changes in 24-hour (d 24) or Dinamap (d Din) measurements of systolic blood pressure (SBP and diastolic BP (DBP) and the corresponding changes in BP measured using conventional techniques (d Con).

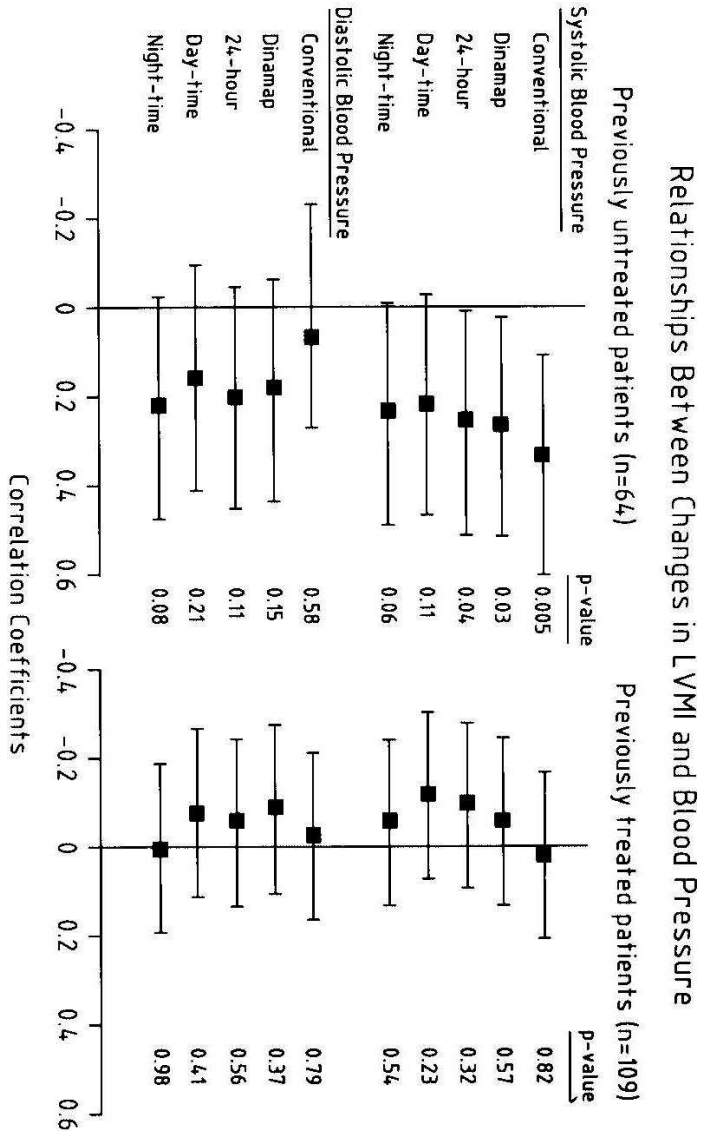


Figure 5.3. Partial correlation coefficients with 95% confidence intervals between changes in left ventricular mass index (LVMI) and changes in blood pressure (BP) after 4 months of treatment in previously untreated and previously treated hypertensives of African ancestry.

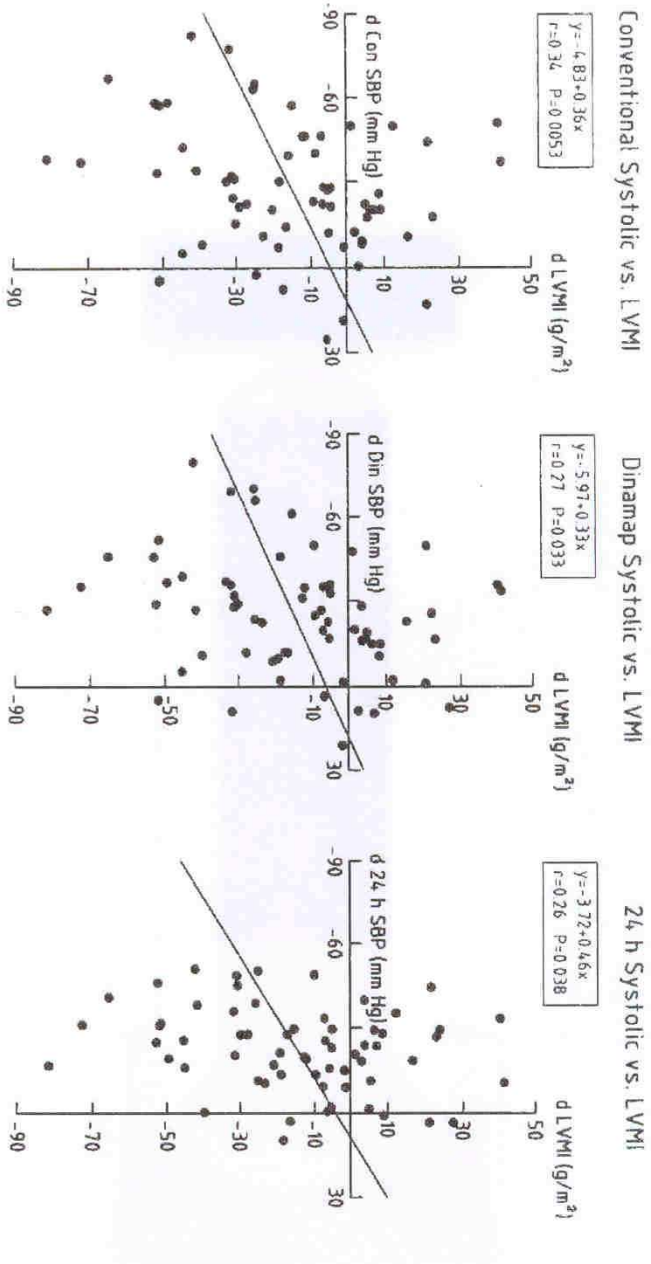


Figure 5.4. Relationships between the changes in left ventricular mass index (LVMI) and in systolic blood pressure (SBP) as assessed by three techniques of BP measurement in previously untreated hypertensive patients of African descent. D Con, conventional measurements; d Din, Dinamap measurements; d 24, 24-hour measurements.

Table 5.4. Regression coefficients between changes in LVM index and in BP over 4 months.

	Systolic Pressure		Diastolic Pressure	
	Regression Coefficient (95% CI)	p	Regression Coefficient (95% CI)	p
Previuosly untreated (n=64)				
Conventional	0.37 (0.14-0.61)	0.004	0.14 (-0.32-060)	0.56
Dinamap	0.34 (0.05-0.63)	0.03	0.42 (-0.12-0.97)	0.13
24-hour	0.46 (0.03-0.89)	0.04	0.60 (-0.013-1.34)	0.11
Daytime	0.34 (-0.05-0.73)	0.10	0.42 (-0.027-1.10)	0.24
Nighttime	0.40 (-0.01-0.81)	0.06	0.55 (-0.06-1.17)	0.08
Previuosly treated (n=109)				
Conventional	0.02 (-0.18-0.23)	0.82	-0.05 (-0.45-0.34	0.80
Dinamap	-0.06 (-0.28-0.15)	0.57	-0.21 (-0.66-1.24)	0.37
24-hour	-0.17 (0.48-0.14)	0.32	-0.17 (-0.73-0.39)	0.56
Daytime	-0.19 (-0.50-0.12)	0.23	-0.22 (-0.75-0.30)	0.41
Nighttime	-0.09 (-0.38-0.20)	0.54	-0.53 (-0.39-0.48)	0.98

5.3.3 Results in Previously Treated Patients

The number of patients that remained on monotherapy was 40 of 65 in the nifedipine-treated group, 14 of 17 in the verapamil SR-treated group, 3 of 14 in the enalapril-treated group, and 5 of 13 in the hydrochlorothiazide-treated arm. There were no significant differences in the use of study medications between previously untreated and treated patients ($p>0.42$). Furthermore, at 4 months the clinic, Dinamap and ambulatory BP (Table 5.2 and Figure 5.1) had fallen to the same extent as in the previously untreated group. After 4 months of antihypertensive therapy with the study medications, LVM and LVM index had decreased by 34 g ($p<0.001$) and 19 g/m^2 ($p<0.001$), respectively (Table 5.3). This was achieved through a reduction in wall thickness and left ventricular end-diastolic diameter. Treatment-induced changes in all echocardiographic measurements were similar ($p>0.18$) in previously untreated and treated patients (Table 5.3). However, in contrast to the previously untreated group, in treated patients, all correlations between the changes in LVM index and any type of BP measurement failed to reach statistical significance (Table 5.4 and Figure 5.3). Adjustment for previous treatment with diuretics or other drugs did not alter these findings.

5.3 DISCUSSION

The Baragwanath Hypertension Study was a single-center trial that investigated the efficacy of various drug classes to initiate antihypertensive treatment in patients of African dsecent (Sareli et al 2001). The same trained research nurse obtained all conventional BP readings. Only patients with sustained hypertension were enrolled. The study medications were titrated or combined to reduce the daytime diastolic BP to a level below 90 mm Hg. Four months of antihypertensive treatment significantly lowered clinic,

24-hour, daytime, and nighttime BP, which led to a significant decrease in wall thickness, LVM, and LVM index.

Significant and positive correlations between the changes in LVM index and all types of systolic BP in response to treatment in previously untreated patients were noted, whereas in previously treated patients these correlations were nonsignificant. Furthermore, in untreated patients, regression of LVM index was not significantly better correlated with the reduction in 24-hour, daytime, or nighttime systolic pressure than with the decrease in the conventional systolic pressure. The latter observations are at variance with two previous studies. In the Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation (SAMPLE) (Mancia et al 1997), after 12 months of follow-up of 184 patients, the decreases in systolic/diastolic pressure were 26/18 mm Hg for the clinic pressure and 18/12 mm Hg for the 24-hour pressure. LVM index decreased from 158 to 133 g/m^2. The reduction in LVM index was not correlated with the changes in the clinic BP ($r=0.11/0.11$), but it was significantly ($p<0.01$) correlated with the changes in the 24-hour BP ($r=0.42/0.38$). In the study by Fagard[3] et al (1997) during 6 months of follow-up of 54 patients, the reductions in systolic/diastolic BP were 22/16 mm Hg for the conventional pressure, 19/12 mm Hg for Dinamap measurements performed at the clinic, and 17/11 mm Hg for the 24-hour BP. LVM decreased from 237 to 212 g. Changes in LVM were significantly related to changes in systolic BP. The correlation coefficients, adjusted for sex and body size, amounted to 0.39 and 0.40 for the conventional and automated measurements of clinic systolic pressures, respectively, and to 0.55 for the 24-hour systolic pressure. The 24-hour systolic pressure added 7.4% ($p<0.05$) and 6.2% ($p=0.06$) to the variance of the changes in LVM explained in terms of the conventional and automated measurements of clinic systolic pressures, respectively.

The discordance between the findings of the present study and two previous studies (Mancia et al 1997, Fagard et al 1997[3]) may depend on various factors, such as the characteristics of the study participants, duration of follow-up under treatment with

study medications, precision and standardization of the conventional BP readings, and recruitment of previously treated patients. Earlier studies have demonstrated that under antihypertensive treatment, LVM decreases to a similar extent in Caucasian patients and patients of African descent (Skoularigis et al 1994, Radevski et al 2000). Furthermore, previous studies have demonstrated that three months of antihypertensive treatment is sufficient to maximally reduce LVM (Bielen et al 1992, Fagard et al 1997[1]). However, in the Losartan Intervention For Endpoint Reduction (LIFE) study (Devereux et al 2002) the maximum effect on LVH of antihypertensive treatment was not achieved for at least two years. In the SAMPLE study, the 12-month change in LVM index correlated equally with the change in the 24-hour systolic pressure in previously untreated (r=0.49) and previously treated (r=0.39) patients, whereas such relationships were not observed for the changes in the clinic BP (Mancia et al 1997). However, the clinic BP in the SAMPLE study was the average of only two conventional readings, which were obtained by different observers across 11 centers. Conventional BP readings are more difficult to standardize in multicenter studies. In the present study, only one study nurse measured the clinic BP at baseline and follow-up in all patients. The strength of the reported associations of LVM index with conventional BP readings has varied greatly, with correlation coefficients ranging from close to zero (Balansard et al 1991) to approximately 0.5 (Fagard et al 1992). Fagard[2] et al (1997) produced convincing evidence suggesting that differences among studies may be partly attributable to the variable degrees of standardization and the divergent number of conventional BP readings.

In the Baragwanath Trial, all patients had a daytime diastolic BP ranging from 90 to 114 mm Hg. Patients with white-coat hypertension were therefore excluded. In the two previous studies comparing the strength of the relationships between ambulatory and conventional BP and LVM (Fagard[3] et al 1997, Mancia et al 1997), patients were exclusively selected on the basis of conventional BP readings at the clinic. Furthermore, depending on the number of clinic visits, the number of conventional BP readings averaged to diagnose hypertension, and the level of the conventional BP, the prevalence

of white-coat hypertension among patients with elevated clinic pressure on conventional measurement may range from 5% (Pickering et al 1988) to >70% (Myers and Reeves 1991). In white-coat hypertensive patients, the clinic BP does not reflect the usual BP load and therefore may be expected to be only weakly correlated or not correlated with LVM. We hypothesize that the high degree of standardization of the conventional BP measurements in the clinic and the exclusion of white-coat hypertensive patients explain why in our previously untreated patients, in contrast to earlier studies, the correlations between the changes in LVM and in systolic BP were of similar magnitude for all types of BP measurement.

The limitations of this study are the study sample size, in that sex-specific analysis may have revealed a more important effect of ambulatory as compared to conventional BP in men, but not women.

In conclusion, the results of the present study indicate that in hypertensives of African ancestry, decreases in LVM induced by antihypertensive treatment are correlated with changes in conventional BP equally as well as changes in ambulatory BP. Moreover, there were no differences in the ability of day and night BP to predict changes in LVM in this ethnic group. These data are consistent with the ability of conventional BP to predict LVM as closely as ambulatory BP in cross-sectional studies in this ethnic group.

Chapter 6

A Reduction in Left Ventricular Mass is More Closely Associated with Blood Pressure than with the Use of an Angiotensin-Converting Enzyme Inhibitor in Patients of African Descent.

ABSTRACT

In the reduction of left ventricular mass (LVM), the relative importance of blood pressure (BP) lowering versus the class of antihypertensive employed in groups of African ancestry remains uncertain. In a single-centre, randomized trial I explored the independent associations between LVM and both ambulatory BP and treatment with an angiotensin-converting enzyme inhibitor (ACEI) over a 25-month follow-up period. Patients of African ancestry (n=185 at enrollment) with a mean daytime diastolic BP ranging from 90-114 mm Hg off-treatment were randomized to receive either enalapril, calcium channel blockers (nifedipine or slow release verapamil), or hydrochlorothiazide as initial therapy. Doses were increased and additional therapy, including enalapril, added to achieve a target daytime diastolic BP below 90 mm Hg. At 4, 13 and 25 months of therapy 66, 71 and 72 % of patients had BP values within target ranges. LVM index decreased from 118± 33 g/m^2 at baseline to 101±25, 101±23, and 96±22 g/m^2 at 4, 13 and 25 months of therapy ($p<0.001$ compared to baseline). Accounting for effects of either conventional or ambulatory BP at each time point, the use of enalapril was associated with neither LVM index, nor with LV relative wall thickness over the treatment period. However, in-treatment conventional systolic BP was associated with both LVM index ($p=0.01$) and LV relative wall thickness ($p=0.03$) and systolic night-time BP was associated with both LVM index ($p=0.01$) and LV relative wall thickness ($p=0.005$). In conclusion, in the treatment of hypertension in groups of African origins, the use of an ACE inhibitor confers no additional benefits on LVM beyond that produced by effects on BP.

6.1 INTRODUCTION

As indicated in all preceding chapters, left ventricular hypertrophy (LVH) and concentric remodeling are strong predictors of cardiovascular morbidity and mortality in hypertensive patients (Casale et al 1986; Koren et al 1991; Verdecchia et al 1996; Ghali et al 1998) and in the general population (Levy et al 1990; Levy et al 1994). Moreover, several studies in hypertensive patients have demonstrated that regression of hypertensive LVH is associated with improved prognosis (Levy et al 1994; Muiesan et al 1995; Verdecchia et al 1998; Mathew et al 2001; Devereux et al 2004[2]). Thus, in the treatment of hypertension, regression of LVH and normalization of LV geometry are desirable clinical end-points.

Small sample sizes, a short duration of follow-up and echocardiographic measurements unblinded for the patient's treatment status limit the validity of many previous studies designed to assess the impact of antihypertensive agents on the regression of LVH (Dahlöf et al 1992; Schmieder et al 1998; Klingbeil et al 2003; Neaton et al 1993; Gottdiener et al 1997). Quantitative reviews of the literature, of which one included open and uncontrolled studies, have suggested that angiotensin-converting enzyme (ACE) inhibitors (Dahlöf et al 1992; Schmieder et al 1998) and angiotensin II receptor blockers (Dahlöf 2001) might be particularly effective in regressing LVH, whilst β-adrenoreceptor blockers would be least effective. In the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial conducted in hypertensive patients with electrocardiographic evidence of LVH, the angiotensin II receptor blocker, losartan, was more effective at regressing LVH than the β-adrenoreceptor blocker, atenolol, an effect that was independent of office BP (Devereux et al 2004[1]; Okin et al 2003). However, in a small cohort of other ethnic groups, mostly consisting of patients of African ancestry, a significant decrease in LVM was not achieved with losartan (Devereux et al 2004[1]).

The lack of ability of losartan to decrease LVM to a greater extent than atenolol in patients of African descent in the LIFE study (Devereux et al 2004[1]) was also mirrored by

an inability of losartan to produce greater effects on CV outcomes as compared to atenolol in African-Americans patients (Julius et al 2004). Indeed the overall analysis on CV outcomes favored atenolol as opposed to losartan (Julius et al 2004). The ethnic-specific effects of agents that block the RAS on CV outcomes were also noted in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). In the ALLHAT study, in which 35% of the patients enrolled were African-Americans, a significant interaction between ethnic group and treatment was noted when comparing the ACE-I, lisinopril, to the diuretic treatment group with respect to stroke and CVD, with lisinopril achieving a worse outcome in patients of African ancestry (Julius et al 2004).

The lack of appreciable benefit on target organ effects of ACE-I therapy over that of other therapeutic classes in patients of African descent, was also noted in the Baragwanath Hypertension Study, a single-centre randomized trial that compared several drug classes (Sareli et al 2001). In this study (Sareli et al 2001) the use of an ACE-I conferred no appreciable benefit over that of other antihypertensive classes of agents in reducing LVM over a four-month treatment period. However, maximal decreases in LVM may require treatment for up to two years (Devereux et al 2002). Consequently, the aim of the present study was to assess the independent associations between LVM and both ambulatory BP and treatment with an ACE-I over a 25-month follow-up period in the Baragwanath Hypertension Study.

6.2 METHODS

6.2.1 Study design and subjects.

The Committee for Research on Human Subjects of the University of the Witwatersrand approved the study (clearance number M940106). Patients gave informed written consent. The Baragwanath Hypertension Study was a single centre, prospective, randomized, open-label, actively controlled study, conducted at the Chris Hani-

Baragwanath Hospital from 1994 until 1998. The study design, and inclusion and exclusion criteria have been described in detail (chapter 6) (Sareli et al 2001). The antihypertensive therapy; assessment of the patient's adherence to the prescribed medication, and the number of follow-up visits to achieve BP control employed in the study, have also been previously reported (chapter 6, Sareli et al 2001). Briefly, patients diagnosed as being hypertensive after a 2-week placebo run-in period and with a count of returned placebo tablets within 80 to 120% of the expected number qualified for randomization, if daytime diastolic BP was 90-114 mm Hg.

Eligible patients were randomized to receive either nifedipine 30 mg/day as a gastrointestinal therapeutic system (GITS) formulation, verapamil slow release (SR) 240 mg/day, hydrochlorothiazide 12.5 mg/day, or enalapril 10 mg/day (Sareli et al 2001). Patients were followed up at monthly intervals and if the target BP (daytime diastolic BP<90 mm Hg) was not achieved, the daily dose of the initial agent was increased to 60 mg/day for nifedipine GITS, 360 mg/day for verapamil SR, 25 mg/day for hydrochlorothiazide, and 20 mg/day for enalapril. At 2 months if patients had not achieved target BP, patients receiving nifedipine GITS were randomized to one of four treatment strategies involving either the addition of enalapril (10 mg/day), carvedilol (25 mg/day), or verapamil SR (120 mg/day) or increasing the daily dose of nifedipine GITS to 90 mg/day. In patients with uncontrolled BP originally assigned to receive verapamil SR, the dose was increased to 480 mg/day and then these patients subsequently received hydrochlorothiazide 12.5 mg/day with the possible addition of enalapril 10mg/day. Those originally receiving hydrochlorothiazide 25 mg/day with uncontrolled BP received reserpine 0.125 mg/day with the possible addition of enalapril 10mg/day if necessary to achieve the target BP. Those originally on treatment on enalapril 20 mg/day and with uncontrolled BP subsequently received hydrochlorothiazide followed by nifedipine GITS if indicated.

Of the 409 patients randomized, 233 patients had high quality echocardiograms at baseline and were therefore eligible for inclusion in the current echocardiography

substudy. Of the latter patients, 23 (10%) had been withdrawn at 4 months and 25 did not have measurements at 4, 13 and 25 months. The remaining 185 participants studied had similar BP values at entry and the same proportion of previously treated patients (61% versus 56%, p=0.32). However, the remaining participants were younger (51±10 versus 56±9 years, p<0.0001) and less obese (body mass index = 30±6 versus 32±8 $kg.m^2$, p<0.02) (chapter 6) (Skudicky et al 2002).

6.2.2 Blood pressure measurements and echocardiography.

Conventional and oscillometric clinic BP, ambulatory BP and echocardiographic measurements were performed at baseline and repeated at 4, 13 and 25 months using methods described in chapters 2-5. Echocardiograms were analyzed according to the American Society of Echocardiography convention (Sahn et al 1978). All measurements were recorded on videotape by experienced technologists and analyzed by an investigator who was unaware of the BP, treatment arm and clinical data of the patients. Intra- and inter-observer variability for LVM has been reported on (chapter 5). LVM was derived according to an anatomically validated formula (Devereux et al 1986) and indexed for body surface area. Left ventricular relative wall thickness (RWT) was calculated as previously described (Ghali et al 1998). Left ventricular hypertrophy was diagnosed if LVMI was >120 g/m^2 in males and >100 g/m^2 in females. These criteria were used to define LVH, instead of the thresholds defined in chapter 2, as they are based on mortality data rather than on data obtained from healthy populations. Concentric LVH was diagnosed in persons with LVH and RWT>0.44 for men and women (Ganau et al 1992). Patients with LVH, but without a concentric LV were classified as having eccentric LVH.

6.2.3 Data analysis.

Database management and statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc, Cary, NC). All data are expressed as mean±SD. Proportions were compared using Fisher's exact test. An ANOVA was used to compare data at baseline between groups. The within-group and between-group changes in continuous measurements during follow-up were analysed using the PROC MIXED procedure as implemented in the SAS package. The maximum likelihood approach accounts for randomly missing observations and allows adjustments for baseline values and other covariates (age, gender and body mass index). To assess the BP-independent impact of ACE inhibitors on the on-treatment LVMI and LV RWT, patients were grouped according to whether they were receiving 1) enalapril either as initial therapy or at follow-up (group 1); 2) hydrochlorothiazide as initial therapy or at follow-up, but without enalapril (group 2); 3) nifedipine GITS as initial therapy or at follow up, but without enalapril (group 3), and 4) verapamil SR as initial therapy or at follow up, but without enalapril (group 4). In further analysis all patients who had received calcium channel blockers both initially and during follow-up were combined (groups 3 and 4).

6.3 RESULTS

6.3.2 Study group characteristics.

Of the 185 patients, 173 had optimal echocardiographic data at 4 months. Subsequently, 36 patients were lost to follow-up, 11 were withdrawn for poor blood pressure control, 15 withdrew consent, 2 died, 3 became pregnant, 4 were withdrawn for adverse events and 21 patients did not have optimal echocardiographic recordings at 25 months. The study group largely consisted of women with a high body mass index (Table 6.1). Most patients had no prior record of antihypertensive medication use (Table 6.1).

The baseline demographic and clinical characteristics of the group (n=81, 44%) still remaining to follow-up at 25 months were similar to the total group included in the echocardiography substudy (Table 6.1).

6.3.3 Blood pressure and antihypertensive medication.

The majority of patients received two or more agents (Table 6.2). The number of patients receiving enalapril either as initial therapy or at follow-up (group 1); hydrochlorothiazide as initial therapy or at follow-up, but without enalapril (group 2); and either nifedipine or verapamil SR as initial therapy or at follow up, but without enalapril (groups 3 and 4), are given in Table 6.3.

Maximal ambulatory BP control was largely achieved by 4 months of therapy (Tables 6.2 and 6.3). No further decline in mean ambulatory BP or improvement in the control rate of the ambulatory BP occurred from 4 until 25 months (Table 6.2). However, beyond month 4 we observed a further decline in the conventional clinic based pressures (Table 6.2). At 4 months, patients who had received either nifedipine or hydrochlorothiazide, achieved lower 24-hour, daytime and nocturnal systolic and diastolic BP than those who had been randomized to enalapril or subsequently received enalapril therapy (Table 6.3). Although patients receiving verapamil SR as initial therapy also had a higher ambulatory BP at 4 months, the difference was not statistically significant from the nifedipine and hydrochlorothiazide treated groups. With the addition of subsequent therapy, all groups achieved similar BP values (Table 6.3).

Table 6.1. Baseline demographic and clinical characteristics of the patients.

	All patients with echocardiograph data	Patients remaining at the end of study
Number	185	81
Age (years)	51±10	52± 11
Women (number [%])	143 (77%)	69 (85%)
Weight (kg)	76±15	77±15
Body mass index (kg/m^2)	30±6	31±6
Total cholesterol (mmol/L)	5.1±1.2	5.2±1.2
Glucose (mmol/L)	5.3±2.5	5.6±3.1
Potassium (mmol/L)	4.1±0.4	4.0±0.4
Creatinine (mmol/L)	65±26	67±29
Antihypertensive medication before enrollment (n, %)	112 (61%)	50 (62%)

Table 6.2. Blood pressures (BP), antihypertensive use and proportion of patients with BP control during follow-up.

Months	0	4	13	25
n	185	173	111	81
Conventional BP (mm Hg)	171±19/102±8	148±219/92±11*	135±18/85±10 *	134±21/87±10*†
24 hour BP (mm Hg)	151±15/97±7	130±15/84±9*	126±12/80±8*	128±14/81±8*
Daytime BP (mm Hg)	155±15/102±8	133±15/88±10*	130±13/85±9*	132±15/86±9*
Night-time BP (mm Hg)	144±19/88±10	124±17/76±11*	123±13/76±8*	124±16/76±9*
% (sample size) with				
daytime BP < 140/90 mm Hg	0	61 (106)	68 (76)	62 (50)
daytime BP <90 mm Hg	0	66 (114)	71 (79)	72 (58)
% two or more agents	0	42	48	53
% calcium channel blockers	0	76	82	80
% diuretics	0	28	32	41
% ACEIs	0	18	23	31
% β-blockers	0	6	7	9

*p<0.001 versus baseline, † p<0.001 versus 4 months.

Table 6.3. Blood pressure at baseline and follow-up by treatment group.

Months	0	4	13	25
	Patients receiving enalapril (group1)			
Sample number	47	45	29	25
Median Dose (mg)	10	20	20	20
Conventional BP (mm Hg)	169±23/102±11	147±23/92±13*	133±18/85±9*	133±21/86±10*
24 hour BP (mm Hg)	153±16/98±7	136±17/88±10*†	126±12/81±8*	128±16/80±9*
daytime BP (mm Hg)	156±17/103±8	138±16/92±11*†	129±12/85±9*	132±14/86±8*
night-time BP (mm Hg)	145±18/89±9	130±19/81±12*†	123±13/76±8*	123±18/74±10*
	Patients receiving hydrochorothiazide, but not enalapril (group 2)			
Sample number	21	20	15	11
Median Dose (mg)	12.5	25	25	25
Conventional BP (mm Hg)	170±18/103±7	142±19/88±11*	138±24/86±12*	128±11/86±9*
24 hour BP (mm Hg)	147±11/95±7	128±13/82±8*	126±12/80±7*	125±14/79±7*
daytime BP (mm Hg)	149±11/99±6	131±14/86±9*	129±14/84±9*	129±14/84±8*
night-time BP (mm Hg)	140±15/84±10	121±14/73±10*	123±13/76±8*	121±14/74±6*

*p<0.001 versus baseline values; † p<0.05 versus group 2 and 3.

Table 6.3 continued. Blood pressure at baseline and follow-up by treatment group.

Months	0	4	13	25
	Patients receiving nifedipine, but not enalapril (group 3)			
Sample number	92	86	55	34
Median Dose (mg)	30	60	60	60
Conventional BP (mm Hg)	174±17/102±8	148±21/92±10*	132±17/85±8*	135±22/85±11*
24 hour BP (mm Hg)	152±14/97±7	126±11/81±7*	126±13/80±8*	128±14/81±7*
daytime BP (mm Hg)	156±14/103±7	129±12/86±8*	130±14/85±8*	131±15/86±8*
night-time BP (mm Hg)	144±19/89±11	119±13/74±9*	122±14/75±7*	123±14/76±8*
	Patients receiving verapamil, but not enalapril (group 4)			
Sample number	25	22	12	11
Median Dose (mg)	240	360	360	240
Conventional BP (mm Hg)	169±18/102±7	153±21/97±11*	146±15/89±13*	145±23/91±10*
24 hour BP (mm Hg)	151±17/96±7	135±18/85±10*	130±12/81±11*	134±15/85±12*
daytime BP (mm Hg)	152±17/100±8	134±22/87±13*	132±13/84±12*	137±17/89±14*
night-time BP (mm Hg)	144±21/89±10	135±18/81±9*	128±12/78±11*	133±19/80±12*

*p<0.001 versus baseline values.

6.3.4 LV mass and relative wall thickness.

In the study group at baseline 50 % of patients had concentric LVH (n=92), and 15% eccentric LVH (n=28). There was a significant change in LVMI over time (Table 6.4, $p<0.001$). After 4 months of antihypertensive therapy, LVM and LVMI had decreased by 30±49 g and 17± 28 g/m^2, respectively (Table 6.4). However, from 4 months onwards there was no further statistically significant change in LVMI (Table 6.4). Decreases in LVM were achieved largely by a reduction in the posterior and septal wall thickness, as well as by a modest change in LV end diastolic internal diameter (Table 6.4). At 4 months, 40 patients (23 %) had concentric LVH, and 19 patients (11%) had eccentric LVH. Despite maintaining BP control over the subsequent 21 months of therapy, at the end of the study 20 patients (25%) had concentric LVH, and 10 patients (12.5%) still had eccentric LVH.

6.3.5 Predictors of LV mass and relative wall thickness on treatment.

Changes in LVMI over time tended to be modestly greater in the group of patients receiving hydrochlorothiazide as initial therapy or at follow-up, and who did not receive enalapril as additive therapy, as compared to the other groups (Table 6.5). However, these apparent differences failed to achieve significance (Table 6.5). Indeed, during follow-up, treatment arm was not associated with either LVMI or LV relative wall thickness (Table 6.6). However, conventional and nighttime systolic BP were independently associated with in-treatment LVMI (Table 6.6). Moreover, conventional, 24 hour, daytime and nighttime systolic BP were associated with in-treatment LV relative wall thickness (Table 6.6). Neither daytime, nor 24 hour BP, were independently associated with in-treatment LVM (Table 6.6). Both baseline LVMI and LV relative wall thickness were strong determinants of follow-up LVMI and LV relative wall thickness, respectively (Table 6.6).

Table 6.4. Echocardiograph measurements at baseline and follow-up.

Months	0	4	13	25
Number	185	173	111	81
LV end diastolic diameter (mm)	45.9±6.0	44.8±5.5*	45.1±5.2	44.4±5.2*
LV end systolic diameter (mm)	30.2±5.4	28.8±4.9†	28.5±5.4†	28.9±4.5*
LV posterior wall thickness (mm)	11.4±2.4	10.6±1.8†	10.5±1.8†	10.5±3.2†
LV septal wall thickness (mm)	12.4±2.3	11.4±1.9†	11.5±2.1†	11.3±2.2†
FS (%)	35±7	36±7*	38±11*	35±8
EF (%)	63±9	65±10	67±9*	64±12
LVM (g)	210±64	179±50†	180±43†	170±42†
LVMI (g/m^2)	118±33	101±25†	101±23†	96±22†
RWT (ratio)	0.51±0.14	0.48±0.11*	0.47±0.11*	0.47±0.12*
LVH [%, (n)]	65 (120)	34 (59)†	43 (48)†	38 (31)†

LV, left ventricle; FS, LV endocardial fractional shortening; EF, LV ejection fraction; LVM, LV mass; LVMI, LV mass adjusted to height; RWT, relative wall thickness; * $p<0.05$ † $p<0.001$ versus baseline values

Table 6.5. Echocardiographic measurements at baseline and follow-up by treatment group.

Months	0	4	13	25
	Patients receiving enalapril (group1)			
Sample number	47	45	29	25
LVEDD (mm)	46.2±5.9	45.9 ± 5.9	45.7 ± 5.2	45.0± 5.*
LVESD (mm)	30.1±5.2	28.5±5.5*	28.4±4.7*	28.1±5.2*
PWT (mm)	11.4±2.1	10.7±2.0	10.3±1.9*	10.4±2.0*
IVS (mm)	12.6±2.1	11.4±2.0†	11.2±2.6†	11.9±2.2*
FS (%)	35.4±6.1	37.8±7.3*	40.2±11.3*	37.4±6.0
EF (%)	64.4±8.4	67.6±9.3*	66.9±9.5	68.2±7.7
LVM (g)	214.6±73.1	188.3±55.7†	177.2±41.0†	181.2±43.5†
LVMI (g/m^2)	119± 38	104±30†	100±27†	100±23†
RWT (ratio)	0.50±0.11	0.48±0.12	0.46±0.13	0.47±0.12
	Patients receiving hydrochorothiazide, but not enalapril (group 2)			
Sample number	21	20	15	11
LVEDD (mm)	47.0±5.6	44.7 ± 5.9	44.9 ± 4.8	43.9± 5.7
LVESD (mm)	31.3±5.1	29.3±4.9	29.0±3.0	29.3±4.1
PWT (mm)	11.1±2.7	10.0±1.5*	10.6±2.2	9.7±1.2*
IVS (mm)	12.1±2.5	11.5±1.9	11.2±1.8*	10.3±1.4*
FS (%)	33.5±8.6	34.2±6.1	31.6±10.3	33.1±7.1
EF (%)	62.2±12.2	63.3±9.1	63.7±9.8*	61.6±9.5
LVM (g)	208.0±62.4	172.3±47.6*	176.1±34.3*	149.8±29.7†
LVMI (g/m^2)	115±32	94±21*	98±22*	85±18†
RWT (ratio)	0.48±0.15	0.45±0.10	0.48±0.13	0.45±0.11

†p<0.001, * p<0.05 versus baseline values. LVEDD, left ventricular end diastolic diameter; LVESD, LV end systolic diameter; PWT, LV posterior wall thickness; IVS, Interventricular septal wall thickness. See table 4 for other abbreviations.

Table 6.5 continued. Echocardiographic measurements at baseline and follow-up by treatment group.

Months	0	4	13	25
	Patients receiving nifedipine, but not enalapril (group 3)			
Sample number	92	86	55	34
LVEDD (mm)	46.2±6.3	44.8 ± 5.6*	44.8 ± 5.3	44.3± 5.2
LVESD (mm)	30.5±5.1	29.1±4.8*	28.5±6.3*	29.3±4.5
PWT (mm)	11.5±2.3	10.5±1.6†	10.3±1.6†	10.2±2.0†
IVS (mm)	12.3±2.4	11.3±1.9†	11.6±1.9*	11.3±2.5*
FS (%)	34.8±6.9	35.7±7.2	39.0±10.6*	33.7±9.0
EF (%)	63.4±8.9	64.3±9.7	67.0±9.2*	61.1±14.8
LVM (g)	211.2±63.5	177.0±50.4†	176.5±43.5†	169.0±44.3†
LVMI (g/m^2)	120±33	101±24†	101±22†	98±24†
RWT (ratio)	0.51±0.14	0.48±0.10*	0.47±0.10*	0.47±0.13*
	Patients receiving verapamil, but not enalapril (group 4)			
Sample number	25	22	12	11
LVEDD (mm)	43.0±5.1	42.5 ± 3.5	45.1 ± 5.3	43.9± 4.5
LVESD (mm)	28.7±7.1	27.7±4.1	27.8±5.5	28.3±4.0
PWT (mm)	11.8±2.9	11.2±1.8	11.2±1.8	10.8±2.0
IVS (mm)	12.8±2.0	11.7±1.7*	12.2±1.7	11.2±2.1*
FS (%)	34.6±6.7	34.8±7.9	38.2±7.0	35.5±5.8
EF (%)	63.8±8.9	63.8±10.3	68.9±7.7*	64.1±8.5
LVM (g)	195.5±47.2	173.5±34.2*	198.1±52.8	171.3±37.8*
LVMI (g/m^2)	110±23	99±19*	108±26	98±16*
RWT (ratio)	0.56±0.20	0.53±0.10	0.50±0.10	0.50±0.11

†p<0.001, * p<0.05 versus baseline values.

Table 6.6. Predictors of on-treatment left ventricular (LV) mass indexed for body surface area and relative wall thickness (RWT).

	LVMI (g/m^2)		RWT (ratio)	
Characteristics	Estimate±SEM	p-value	Estimate±SEM	p-value
	Model with Conventional BP			
BMI (g/m^2)	-0.27± 0.22	0.23	0.21±0.11	0.072
Age (years)	0.09±0.13	0.85	0.17±0.12	0.008
Gender (female)	5.3±3.3	0.11	0.74±1.72	0.66
Treatment group	-1.6±4.3	0.71	-1.48±2.28	0.52
Baseline LVMI /RWT	0.35±0.04	<0.0001	0.14±0.05	0.003
Systolic BP (mm Hg)	0.13±0.05	0.010	0.06±0.03	0.033
	Model with 24-hour BP			
BMI (g/m^2)	-0.26± 0.22	0.24	0.21±0.11	0.072
Age (years)	0.09±0.13	0.50	0.20±0.07	0.005
Gender (female)	5.7±3.3	0.09	0.76±1.71	0.66
Treatment group	-2.9±4.4	0.51	-3.8±2.6	0.56
Baseline LVMI /RWT	0.35±0.04	<0.0001	0.13±0.05	0.007
Systolic BP (mm Hg)	0.15±0.08	0.07	0.12±0.04	0.005
	Model with day BP			
BMI (g/m^2)	-0.24± 0.22	0.29	0.22±0.12	0.06
Age (years)	0.10±0.13	0.46	0.20±0.07	0.005
Gender (female)	5.7±3.3	0.09	0.85±0.72	0.62
Treatment group	-3.3±4.4	0.45	-4.04±2.6	0.49
Baseline LVMI/RWT	0.35±0.04	<0.0001	0.13±0.05	0.006
Systolic BP (mm Hg)	0.06±0.08	0.41	0.09±0.04	0.017
	Model with night BP			
BMI (g/m^2)	-0.32± 0.22	0.16	0.20±0.12	0.097
Age (years)	0.09±0.13	0.50	0.19±0.07	0.006
Gender (female)	5.8±3.3	0.08	0.83±1.70	0.62
Treatment group	-1.9±4.4	0.66	-3.33±2.65	0.65
Baseline LVMI /RWT	0.34±0.04	<0.0001	0.13±0.05	0.007
Systolic BP (mm Hg)	0.19±0.07	0.010	0.11±0.04	0.005

Combining the groups of patients receiving either nifedipine or verapamil SR as initial therapy or at follow up, and who did not receive either enalapril as additive therapy, revealed the same effects (data not shown).

6.4 DISCUSSION

The main finding of the present study is that in hypertensive patients of African descent treated and followed up for 25 months, several indices of LVH remained positively and independently associated with conventional and nocturnal systolic BP. The use of the ACE inhibitor, enalapril, conferred no appreciable additional benefit on indices of LVH, over that mediated by the decrease in the conventional and nocturnal BP, and its effects did not differ from those of treatment regimens not including an ACE inhibitor.

In the present study the overall reduction in LV mass was ~15% after 4 months and ~17% after 25 months of therapy. Quantitative reviews of randomised, controlled studies of antihypertensive agents of the same class studied by us have reported on reductions of LV mass between 8 and 12% over an average treatment period of ~27 weeks (Schmieder et al 1998) and also between ~8 and 16% over an unspecified period (Fagard[3] 1995). More recent original randomized, controlled studies have reported on reductions in LVM of ~11.5% (Devereux et al 2004[1]) and ~11-12.7% (Devereux et al 2001) over one year of treatment and ~16% after 2 years of study (Devereux et al 2004[1], Devereux et al 2002). The apparently greater reduction in LVM noted over a shorter treatment period in the present as compared to previous studies (Schmieder et al 1998, Devereux et al 2004[1], Fagard[3] 1995; Devereux et al 2001; Devereux et al 2002) could be explained by a higher proportion of patients being treated to target diastolic (72%) and systolic (62%) BP, than in other studies (for example ~40% of patients were treated to target BP in the LIFE study [Dahlöf et al 2002[1]]).

Few studies, all with small sample sizes, have reported on reductions in LVM on-treatment in mild-to-moderate hypertension in patients of only African descent

(Skoularigis et al 1994, Middlemost et al 1994, Roman et al 1998). The longest period of follow-up in these studies was three months (Skoularigis et al 1994). Nevertheless, the degree of change in LVM index reported on in the present study is consistent with that previously shown to occur after three months of treatment (~16-19%) (Skoularigis et al 1994, Middlemost et al 1994). In these studies (Skoularigis et al 1994, Middlemost et al 1994) ambulatory BP was also used to define BP control and subsequently uptitrate or assign additional therapy. In a previous study conducted where a large proportion of the study sample consisted of African-Americans, LVM decreased at most by ~7% over six months of treatment (Roman et al 1998). A potential explanation for the difference between the present study and this prior study (Roman et al 1998) is not apparent.

The present study is the first large-scale study to formally explore the relative importance of drug class versus BP lowering as determinants of in-treatment LVM reduction in a group of African ancestry. In this regard, LVM decreased to a similar degree in all study groups and was associated with a decline in nocturnal BP. In contrast to the present study, a meta-analysis of 109 studies including open and uncontrolled studies, has suggested that treatment-induced reductions in LVM were greater with ACE inhibitors than with other drug classes despite similar reductions in conventional BP (Dahlöf et al 1992). However, subsequent quantitative reviews of studies of a high scientific quality have not supported the contention that ACE inhibitors are more effective than calcium channel blockers or diuretics at reducing LVM (Schmieder et al 1998, Fagard[3] 1995). More recent original studies comparing ACE inhibitor and calcium channel blocker therapy also showed similar reductions in LVM between these drug classes (Devereux et al 2001). The quantitative effects of ACE inhibitors and calcium channel blockers on LVM reported on in the present study are consistent with those previously shown to occur in hypertensive patients of African descent after 3 months of treatment with enalapril (~19%) and nifedipine (~16%)(Skoularigis et al 1994, Middlemost et al 1994).

The attenuated effect of calcium channel blockers on LVM reduction reported on in early quantitative reviews (Dahlöf et al 1992), and large-scale studies (Gottdiener et al 1997) may be ascribed to the use of non-dihydropyridine rather than dihydropyridine calcium channel blockers. Indeed, in the present study, the non-dihydropyridine calcium channel blocker, verapamil, reduced LVM by only ~7% over a 25-month treatment period. However, although not statistically different, LVM index tended to be lower at baseline and mean ambulatory BP higher on-treatment in the verapamil-treated as compared to the other groups. Moreover, study group was not associated with in-treatment LVM when accounting for baseline LVM index or in-treatment conventional or ambulatory BP in the statistical model.

In-treatment reductions in LVM may be achieved by decreases in LV wall thickness and internal dimensions. In the present study, both LV wall thickness and LV end diastolic diameter were reduced at all time points studied and in each of the treatment groups. However, as indicated by the decrease in LV relative wall thickness at each time point in all study groups, the change in LV wall thickness was comparatively greater than that for LV end diastolic diameter. These changes therefore support the notion that on-treatment reductions in LVM are largely achieved by alterations in wall thickness rather than internal diameters.

A limitation of the present study is that after 25 months of treatment less than half the sample remained in the study. However, this was adjusted for using a proc mixed model in the statistical analysis. A second potential limitation of this study was that it was conducted with an open-label design. Nevertheless, ambulatory BP was employed to account for observer bias in BP measurements, and echocardiographic measurements were analyzed by an investigator unaware of the BP, treatment arm and the clinical data of the patients. Third, statistical analysis was performed on groups to which patients had not necessarily been randomised. This approach was required in order to assess the BP-independent impact of ACE inhibitors on LVM in patients assigned both at randomisation

and during follow-up to receive ACE inhibitors. Fourth, although a high proportion of patients had LVH, this study was not specifically conducted in patients with LVH.

The present study provides insight into new studies being conducted to explore the comparative benefits of antihypertensive agents on target organ damage in patients with mild-to-moderate hypertension. In the light of the development of novel antihypertensive agents designed to block the actions of the renin-angiotensin system (Gradman et al 2005), additional benefits conferred on LVM regression are expected to be mediated largely through reductions in BP in groups of African ancestry at least.

In conclusion, the results of the present study indicate that in the treatment of mild-to-moderate hypertension in groups of African descent, the use of an ACE inhibitor confers no additional benefits on LVM beyond that produced by effects on BP alone. These data would support the notion that therapeutic class of antihypertensive agent is not as important as BP in the reduction of LVM in mild-to-moderate hypertension in groups of African ancestry.

Chapter 7

Changes in Ambulatory Blood Pressure Predict Regression of Left Ventricular Hypertrophy in Patients of African Ancestry Receiving Agents Influencing the Renin-Angiotensin System.

ABSTRACT

Agents that target the renin-angiotensin system (RAS) appear to produce BP-independent effects on LVM. Hypertensives of African ancestry have distinct BP responses to antihypertensives that target the RAS. Whether decreases in BP associated with the use of agents that specifically target the RAS predict regression of LVH in patients of African ancestry is uncertain. Patients with a mean daytime diastolic ambulatory BP (ABP)$\geq$90 mm Hg and LVH on echocardiography received candesartan cilexetil 8-16 mg once daily for 2 months followed by the addition of hydrochlorothiazide 12.5 mg daily for a further month and subsequently ramipril 2.5-5 mg daily for another 2 months if diastolic ABP remained>90 mm Hg. The impact of changes in ABP on alterations in LVM index (LVMI) was assessed. Of the 86 patients starting, 47 completed the study. Candesartan monotherapy produced only modest decreases in ABP (from 153$\pm$17/95$\pm$6 to 151±18/93±7 at 2 months, $p<0.05$). The addition of a diuretic resulted in a striking decrease in ABP (to 139±21/87±9 at 3 months, $p<0.0001$ versus baseline), an effect that was only partially augmented by the addition of ramipril ($p<0.05$). LVMI decreased from 122±20 to 111±23 g/m^2 ($p<0.005$) with treatment. Adjusting for gender, changes in systolic ABP (daytime, $r=0.46$, $p=0.006$) were predictive of changes in LVMI. In conclusion, these results suggest that in hypertensive patients of African ancestry receiving therapy targeting the RAS and a diuretic agent, changes in systolic BP may be an appropriate surrogate for target organ effects.

7.1 INTRODUCTION

As underscored throughout the present thesis, LVH is an independent predictor of CV mortality and morbidity in patients with hypertension (Levy et al 1990, Koren et al 1991). A decrease in LVM following the use of antihypertensive therapy is associated with beneficial effects on the vasculature, the incidence of arrhythmic events, cardiac dysfunction and morbidity and mortality in hypertensive patients, effects that have frequently been reported to be independent of conventional BP (Hansson et al 1991; Gonzalez-Fernandez et al 1993; Grandi et al 1989; Dahlof et al 2002[2]). Hence, regression of LVM is a crucial clinical indicator of beneficial effects of antihypertensive agents. As highlighted in chapter 1 and in the previous chapter, recent evidence suggests that regression of LVH and the associated improvements in CV outcomes following the use of angiotensin II (AII) receptor antagonists and angiotensin converting-enzyme inhibitors (ACE-I) is to some extent independent of BP changes in hypertensive patients (Dahlof et al 2002 [2], Okin et al 2003, Malmqvist et al 2001). The outcome of these studies (Dahlof et al 2002 [2], Okin et al 2003, Malmqvist et al 2001) raises the question of whether changes in BP following the use of AII receptor antagonist and ACE-Is, are an appropriate clinical index of modifications in target organ damage in hypertensives.

Recent evidence in patients of European ancestry indicates that changes in BP following the use of an AII receptor blocker are indeed associated with reductions in LVM in patients with LVH (Nystrom et al 2002). Whether this effect is noted in all populations, in particular populations of African ancestry whose BP responses to blockers of the renin-angiotensin system (RAS) are quite distinct from other groups (Sareli et al 2001, Woodiwiss et al 2006), has not been determined. Indeed, previous data from our group suggests that the use of an ACE-I may result in a reduction in LVM in hypertensives of African ancestry in association with little change in BP (Middlemost et al 1994). Although, in the previous chapter of the present thesis I was able to demonstrate that the use of an ACE-I produced no appreciable benefit over that of BP changes in mediating a reduction

of LVM over a 25 month treatment period, in this study, patients were not selected for the presence of LVH. Consequently, further studies are required to ascertain whether potential class-specific effects of RAS blockers on LVM mask BP effects on the regression of LVH in groups of African ancestry. The question of whether decreases in BP predict regression of LVH is of particular importance in groups of African ancestry who have a higher prevalence of LVH (Danzer et al 2005) and in whom electrocardiograph criteria are poor indicators of LVH (Lee et al 1992), thus necessitating the use of other clinical indicators of regression of LVH.

In the present study I therefore assessed the relationship between changes in BP and alterations in LVM following the use of agents that target the RAS (an AII receptor blocker and an ACE-I) used together with a diuretic agent, in hypertensives of African ancestry with LVH. Both an AII receptor blocker and an ACE-I were studied as a degree of synergy exists in this combination (Mogensen et al 2000).

7.2 METHODS

7.2.1 Patients, study design and blood pressure measurement

This was a single center, prospective, open-label study, conducted at Chris Hani-Baragwanath Hospital from 1999 through to 2001. Men and women aged 21-to-70 years, without significant concomitant cardiovascular or non-cardiovascular disease, but who nevertheless had LVH as determined from echocardiograms, were recruited. Women of reproductive age had to apply appropriate contraception. All patients gave written informed consent before inclusion into the study.

Patients were initially screened using a Dinamap 1846 SX vital signs monitor (Critikon Inc, Tampa, FL) as previously described (Borrow et al 1982). If the mean diastolic BP was $\geq$90 mm Hg (10 measurements over 30 minutes taken in a sitting position) the patients underwent echocardiography to determine the presence of LVH.

LVH was defined as a LVM indexed to body surface area (LVMI) >120 g/m^2 in males and >100 g/m^2 in females. These criteria were used to define LVH, instead of the thresholds defined in chapter 2, as they are based on mortality data rather than on data obtained from healthy populations. Patients fulfilling inclusion and exclusion criteria underwent a two-week washout period followed by a two-week placebo run-in phase. Patients whose mean diastolic BP remained $\geq$90 mm Hg on Dinamap measurements then had 24 hour ambulatory BP monitoring performed using a SpaceLabs model 90207 oscillometric device (SpaceLabs Inc, Redmond, WA), programmed to obtain readings every 15 minutes from 6.00 to 18.00h and every 20 minutes from 18.00 to 6.00h (O'Brien et al 1991) . Patients whose mean ambulatory daytime diastolic BP was ≥90 mm Hg and ≤110 mm Hg and mean daytime systolic BP was ≤180 mm Hg were subsequently considered eligible. Patients were excluded if their medication compliance during the placebo run-in phase was poor (<80% or >120% of the expected tablet count).

Eligible patients received candesartan cilexetil 8 mg once daily and if after a month BP control was not achieved (office diastolic BP >90mmHg) the dose of candesartan cilexetil was increased to 16 mg. At the end of the first two month period of the study ambulatory BP monitoring was again performed and patients whose mean daytime diastolic BP was <90 mm Hg continued on the same therapy. If daytime diastolic BP <90 mm Hg was not achieved at the end of the initial two month treatment period, hydrochlorothiazide (HCTZ) 12.5 mg once daily was added and ambulatory BP monitoring again performed after another month. If daytime diastolic BP was still ≥90 mm Hg, patients were given ramipril 2.5 mg daily for a month, and the dose increased to 5 mg daily if required. After 5 months final ambulatory BP monitoring and echocardiography were performed. Patients were withdrawn from the study if at any follow-up visit the mean daytime ambulatory BP exceeded 220/114 mm Hg, or if they experienced any serious adverse event whilst receiving combination therapy.

7.2.2 Echocardiography

Two-Dimensional targeted M-mode echocardiograms were obtained with a Hewlett Packard Sonos 2500 system using a 2.5 MHz transducer using techniques described in chapter 2. The echocardiograms were analyzed according to the American Society of Echocardiography recommendations (Sahn et al 1978). Left ventricular mass was derived according to an anatomically validated regression method that corrects LVM estimates obtained from recommended measurements (Devereux et al 1986). In the present study LVM was indexed for body surface area to ensure that LVH was hypertensive and not adiposity-induced. Replicated LVM values obtained by the two persons performing the measurements required to calculate LVMI showed that the inter- and intra-observer coefficients of variation were 12.4% and 11.4% respectively.

7.2.3 Data analysis

Database management and statistical analysis were performed with SAS software, version 8.2 (SAS Institute Inc, Cary, NC). Within-group differences in continuous measurements were tested with repeated measures analysis of covariance with gender as a covariate. Proportions were compared using the Fisher's exact test. Stepwise multiple regression models were used to determine predictors of LVMI and Pearson correlation coefficients between ambulatory BP measurements and LVMI were calculated.

7.3 RESULTS

7.3.1 Baseline characteristics, withdrawals, adverse events and medication

Of 167 patients screened for the study, 86 patients who fulfilled inclusion and exclusion criteria were entered into the study. From the group recruited, 47 patients completed five months of treatment who were included in the analysis. Importantly, the characteristics of the 47 patients who completed the study were similar to the group initially recruited (Table 7.1). Twenty-one of the initial 86 patients recruited were withdrawn because of mean daytime ambulatory BP values that exceeded 200/114 mm Hg on subsequent visits, 7 defaulted, 1 died of a motor vehicle accident, 1 suffered a non-fatal stroke, 2 patients developed anemia and 4 patients an ACEI-related cough. Three patients did not have optimal echocardiograms at the end of the study. During the course of the study 8 patients suffered headaches, 7 articulation aches, and 5 backaches. The study group was mostly female with a high body mass index (Table 7.1). No significant changes in mean values of biochemical parameters at the end of treatment period were noted.

Of the 47 patients included in the analysis, at the end of the treatment period 3 patients remained on monotherapy with 16 mg candesartan daily, 12 patients were receiving 16 mg candesartan and 12.5 mg HCTZ daily, 10 patients were receiving 16 mg candesartan, 12.5 mg HCTZ and 2.5 mg ramipril daily, and the remaining 22 patients were receiving maximum doses of all three agents.

7.3.2 Blood pressure response

In those patients included in the final analysis a continuous decline in BP was noted over the time course of the study (Table 7.2). Monotherapy with candesartan produced only modest BP effects (Table 7.2). After two months of candesartan monotherapy only 2 of 47 patients had achieved BP control, defined as mean daytime ambulatory BP <140/90 mm Hg. However, the addition of HCTZ at two months resulted in a striking decrease in ambulatory BP as determined at 3 months (Table 7.2). Thirty four % of patients (16 of 47) achieved controlled BP values after 3 months of therapy. The

Table 7.1: Baseline characteristics

	Initially recruited n=86	Completed n=47
Gender (% female)	81	83
Age (years)	53.5±10.2	53.3±9.4
Duration of hypertension (years)	4.5±6.3	4.4 ± 6.2
Newly diagnosed (%)	31	32
Body mass index (kg/m^2)	31.5 ± 6.5	31.4 ± 6.6
Serum K^+ (mmol/l)	3.6±0.4	3.7 ± 0.4
Serum glucose (mmol/l)	5.0 ± 2.1	5.1 ± 2.3
Total cholesterol (mmol/l)	5.0 ± 1.1	5.1 ± 1.1
Serum creatinine (µmol/l)	72 ± 15	73 ± 16
Blood Pressure		
Clinic* SBP/DBP (mm Hg)	160 ± 18/98 ± 6	158 ± 16/97 ± 7
24 hour ambulatory SBP/DBP (mm Hg)	154 ± 16/95 ± 6	153 ± 17/95 ± 6

SBP, systolic blood pressure; DBP, diastolic blood pressure.

* Oscillometric measurement.

Table 7.2. Effect of antihypertensive therapy with agents that target the RAS and diuretics on blood pressures in hypertensives of African ancestry.

	Baseline	2 months	3 months	5 months	Change in BP at 5 months
Clinic# SBP/DBP (mm Hg)	158±16/97±7	152±22*/88±8**	140±25/84±11**	132±23/81±10**†	-25±20/-16±11
24 hour ambulatory SBP/DBP (mm Hg)	153±17/95±6	151±18/93±7*	139±21/87±9**	135±20/83±10**†	-18±16/-11± 9
Day ambulatory SBP/DBP (mm Hg)	159±17/100±5	156±17/98±6*	144±22/92±10**	139±20/88±10**†	-19±17/-12±10
Night ambulatory SBP/DBP (mm Hg)	148±19/89±10	145±21/87±10	133±20/87±10**	130± 20/79±10**†	-18±17/-11±11

* p<0.05, ** p<0.0001 versus baseline; † p<0.05 versus 3 months except for night ambulatory SBP. # oscillometric BP.

addition of ramipril only modestly accentuated the decline in BP (Table 7.2). However, with the addition of ramipril, 60% of patients (28 of 47) achieved BP control by the end of the study.

7.3.3 Left ventricular mass

After 5 months of therapy a decrease in LVMI occurred (Table 7.3). Regression of LVH was achieved by a reduction in LV wall thickness and not by a decrease in LVEDD (Table 7.2). Decreases in ambulatory 24 hour, daytime and nighttime systolic BP noted at 5 months were correlated with reductions in LVMI (Figures 7.1 and 7.2). In addition, the decrease in 24 hour, daytime and nighttime systolic BP noted at 5 months, were independent predictors of reductions in LVMI adjusted for gender (24 hour systolic ABP, r=0.46 [Figure 7.2]; daytime systolic ABP, r=0.46, p=0.006 and nighttime systolic ABP, r=0.44, p=0.009). Neither changes in ambulatory 24 hour, daytime nor nighttime diastolic BP values were significantly correlated with decreases in LVMI (Figure 7.1), although a trend effect for a correlation between changes in 24 hour diastolic BP and change in LVMI was noted.

Table 7.3. Effect of antihypertensive therapy with agents that target the renin-angiotensin system and diuretics on echocardiograph measurements in hypertensives of African ancestry with left ventricular hypertrophy.

	Baseline	5 months	Change in values
LVESD (mm)	32.1 ± 6.4	32.1 ± 4.9	-0.02 ± 0.5
LVEDD (mm)	45.8 ± 5.4	47.9 ± 5.5	2.1 ± 3.7*
PWED (mm)	11.5 ± 1.5	10.1 ± 1.8*	-1.4 ± 1.5*
IVS (mm)	13.1 ± 2.3	11.8 ± 1.9	-1.3 ± 2.4*
FS (%)	32 ± 6	33 ± 6	1.1 ± 7.2
EF (%)	60 ± 9	61 ± 8	1.5 ± 9.8
LVM (g)	216 ± 43	193 ± 45	-23 ± 40*
LVMI (g/m^2)	122 ± 20	111 ± 23*	-11 ± 25*
RWT (ratio)	0.51 ± 0.10	0.43 ± 0.10*	-0.08 ± 0.08*

LVESD, left ventricular end systolic diameter; LVEDD left ventricular end diastolic diameter; PWED, posterior wall thickness at end diastole; IVS, interventricular (septal) wall thickness at end diastole; FS, endocardial fractional shortening; EF, ejection fraction; LVM, left ventricular mass; LVMI, LVM index; RWT, relative wall thickness.* $p<0.001$ compared to baseline.

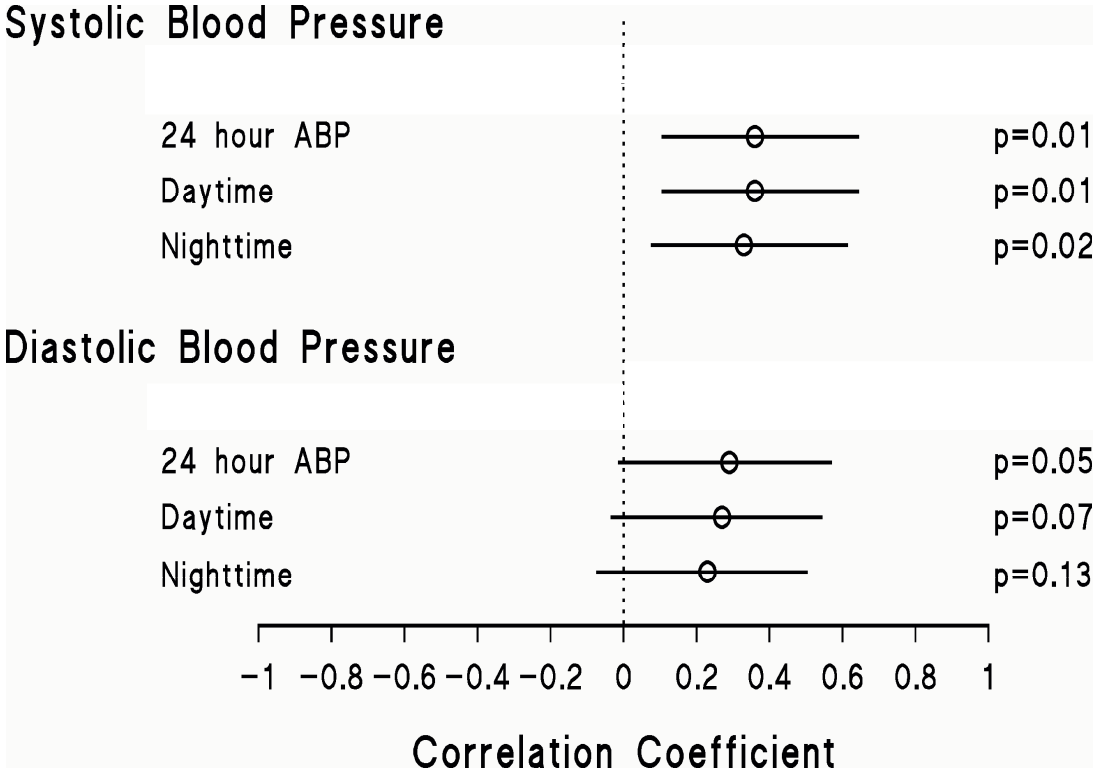


Figure 7.1. Partial correlation coefficients between change in ambulatory (ABP) blood pressure and change in left ventricular mass index following 5 months of antihypertensive therapy with agents that target the renin-angiotensin system together with diuretics given to hypertensive patients of African ancestry with left ventricular hypertrophy.

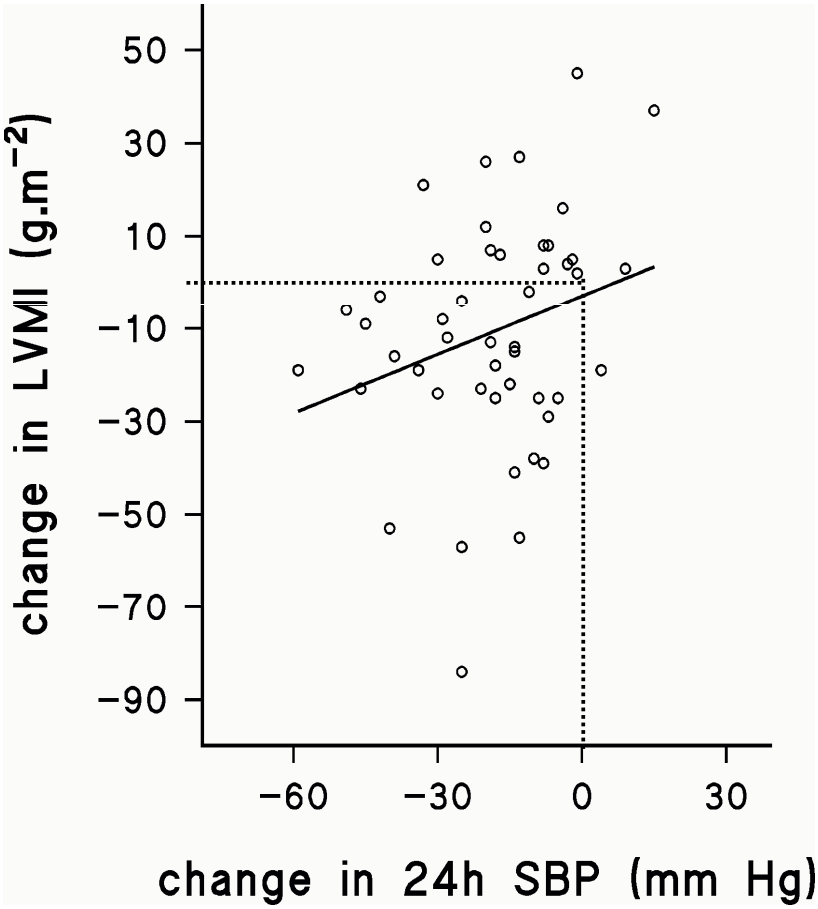


Figure 7. 2. Relationship between change in 24 hour ambulatory systolic blood pressure and change in left ventricular mass index following 5 months of antihypertensive therapy with agents that target the renin-angiotensin system together with diuretics given to hypertensive patients of African ancestry with left ventricular hypertrophy. The correlation coefficient is provided in figure 7.1.

7.4 DISCUSSION

The main findings of the present study are that in hypertensive patients of African ancestry with LVH, changes in ambulatory systolic BP mediated by co-administration of an angiotensin II receptor blocker, candesartan, together with HCTZ (12.5 mg) and the ACE-I, ramipril (in 68 % of patients) predict regression of LVH.

Although decreases in LVM are associated with BP changes in patients of European ancestry receiving antihypertensive agents that target the RAS (Nystrom et al 2002), prior data from our group suggest that decreases in LVM in patients of African origins receiving ACE-Is can occur with little change in BP (Middlemost et al 1994). The question of whether agents that target the RAS mediate effects on LVM in patients of African ancestry that can be predicted by BP changes is of particular importance as the predominant RAS profiles are quite distinct in patients of African ancestry (Luft et al 1991) and BP responses to RAS inhibitors are unique in comparison to other population groups (Sareli et al 2001, Woodiwiss et al 2006). The present study provides clear evidence that in hypertensive patients of African ancestry with LVH, receiving therapeutic agents targeting the RAS, change in ambulatory BP is associated with regression of LVM.

This is the first study to show that in subjects of African ancestry who have a high prevalence of LVH (Drazner et al 2005), BP changes following the use of antihypertensive agents predict regression of LVH irrespective of whether previous therapy had been utilized. Prior studies conducted in this population group have demonstrated that change in ambulatory BP predicts decreases in LVM in newly diagnosed, but not in previously treated patients irrespective of whether LVH was present (Skudicky et al 2002, chapter 5). Although data in previously treated patients of African descent (Skudicky et al 2002, chapter 6) cast doubt on the importance of BP measurements as an appropriate clinical index of target organ effects (specifically LVH) in previously treated patients of this population group, to-date no study has been conducted to assess the impact of changes in BP on LVM in previously treated patients with LVH.

Data from the present study indicate that alterations in BP are indeed an appropriate index of beneficial effects on LVM in previously treated patients (69% of the study group) with LVH.

A potential limitation of the present study is that approximately 45% of patients had to be withdrawn, of which the majority (26%) were withdrawn because daytime ambulatory BP values exceeded 200/114 mm Hg. These data are entirely consistent with the relatively low number of patients of African ancestry that respond to antihypertensive agents that target the RAS (Sareli et al 2001, Woodiwiss et al 2006). Importantly, however, it is also acknowledged that therapeutic agents that target the RAS are efficacious in a proportion of hypertensive patients of African ancestry when used together with diuretic agents (Middlemost et al 1994), as in the present study. The aim of the present study was not to evaluate the efficacy of agents that target the RAS when combined with a diuretic on BP in hypertensive subjects of African ancestry. The question I wished to answer is whether decreases in LVM index are indeed associated with changes in BP mediated by these agents in those patients of African ancestry who respond to these agents. In this regard, in those patients who did not require withdrawal from the study, a marked antihypertensive response was noted, thus allowing for an evaluation of the relationship between LVH regression and BP changes.

As the major change in BP noted in the present study occurred with the addition of the diuretic agent, it may be argued that the relationship between changes in BP and LVM index noted in the present study are attributed to diuretic effects alone and have little to do with RAS blockade. However, diuretic agents at this dose, when used as monotherapy, do not mediate such profound decreases in systolic BP (~12 mm Hg on average in 24-hour systolic BP) in this ethnic group (Skoularigis et al 1995, Sareli et al 2001). Therefore, the impact of antihypertensive therapy on BP and LVM index can only be attributed to combination therapy and thus in-part to RAS blockade.

In summary, the results of the present study indicate that changes in BP are indeed associated with regression of LVH in patients of African ancestry receiving therapeutic agents that target the RAS together with a diuretic agent. These results suggest that BP measurements may be used as a clinical indicator of regression of LVH in hypertensive patients of African ancestry receiving these agents.

Chapter 8

Effect of Slow-release Indapamide and an ACE-I as Compared to Amlodipine on 24-hour Blood Pressure and Left Ventricular Mass Reduction in Hypertensive Patients of African Ancestry.

ABSTRACT

In the treatment of hypertension in subjects of African origins, there is question as to whether diuretic therapy, followed by the addition of an angiotensin-converting enzyme inhibitor (ACE-I) is as effective as calcium channel blockers on BP and LVM. In the present study I therefore compared the effects of slow release (SR) indapamide with the addition of an ACE-I to that of the calcium channel blocker, amlodipine, when used as initial therapy, on BP and LVM over 6 months of treatment in this ethnic group. Patients with mean daytime ambulatory diastolic BP (DADBP) ≥90 mm Hg and ≤110 mm Hg (n=125, age 53 $\pm$ 11, 68% female) were randomized to receive open-label indapamide SR 1.5 mg or amlodipine 5 mg. If DADBP at 1 month was ≥ 90 mm Hg, perindopril 4 mg was added to indapamide SR or the dose of amlodipine was increased to 10 mg. After 1 month, there was an equivalent decline in systolic and diastolic BP in the two groups ($p<0.0001$). In the indapamide SR treated group (n=62) the daytime BP decreased from 153±12/101±6 to 138±15/92±10 and in the amlodipine treated group (n=58) it decreased from 152±13/99±5 to 138±12/91±8. At 6 months DABP decreased to 130±15/86±8 and to 129±11/85±5 mm Hg for the indapamide SR (n=42) and amlodipine (n=44) treated groups respectively. Both groups showed equivalent regression in LVM index. These data suggest that in hypertensive patients of African ancestry initiating therapy with the diuretic, indapamide SR and then adding the ACE-I, perindopril 4 mg is equally as effective as amlodipine therapy at reducing BP and modifying target organ damage.

8.1 INTRODUCTION

As compared to other ethnic groups, in groups of African descent, agents that block the renin angiotensin system (RAS), such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers are not as effective at reducing BP (Cushman et al 2000, The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002, chapter 7) or decreasing LVM (Devereux et al 2004[1], Sareli et al 2001, Radevski et al 1999; Skoularigis et al 1994). In many patients this does not pose a treatment dilemma as the South African Hypertension Society and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) guidelines recommend thiazide diuretics and not RAS blockers as initial therapy for the treatment of uncomplicated hypertension (Hypertension Society of Southern Africa, [Seedat et al 2006], The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2003). However, there are many compelling indications for the use of RAS blockers in the treatment of hypertension, one of which is hypertension with LVH (Hypertension Society of Southern Africa, [Seedat et al 2006], The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2003). As LVH is likely to be highly prevalent in groups of African descent (see chapters 1 and 2), the ethnic-specific effects of RAS blockers may pose a management decision problem. However, a potential solution to this dilemma is to initiate treatment with a diuretic in patients of African ancestry requiring RAS blockers, and then add a RAS blocker, a combination that is thought to be no less efficacious than in other ethnic groups. However, low-dose thiazide diuretic agents do not achieve ambulatory BP control in patients of African descent (Skoularigis et al 1995). Moreover, in a multi-arm combination trial, a dihydropyridine calcium channel blocker (CCB), when used as monotherapy, was shown to be more efficacious than other classes of antihypertensive agents including low dose hydrochlorothiazide (HCTZ) (12.5-25 mg daily), a thiazide diuretic, as determined from 24

hour ambulatory BP monitoring in patients of African ancestry (Sareli et al 2001). Thus, it appears at least from a BP perspective, that efficacious first-line therapy in groups of African descent may not be diuretic agents, but rather CCBs.

Nevertheless, using ambulatory BP monitoring to assess efficacy, our group have recently demonstrated that monotherapy with the diuretic indapamide was superior to low dose HCTZ (Radevski et al 2002) in the management of hypertension in patients of African descent with mild-to-moderate hypertension. Whether indapamide used as initial therapy, with an ACE-I added as additional therapy, mediates equivalent antihypertensive actions and beneficial effects on LVM when compared to dihydropyridine CCB therapy in groups of African descent has not been evaluated. Therefore, in the present study I compared the effect of slow-release (SR) indapamide followed by the addition of an ACE-I, perindopril, to that of the dihydropyridine CCB, amlodipine, on ambulatory BP and LVM in patients of African descent with mild-to-moderate hypertension.

8.2 METHODS

8.2.1 Study population

This was a single-center, open-label, randomized, prospective study, conducted at Chris Hani Baragwanath Hospital, from 2001 through 2002. Men and women, aged 21-70 years, without significant concomitant cardiovascular or non-cardiovascular disease were recruited. Women of reproductive age had to apply adequate contraception. All patients gave written informed consent before inclusion into the study.

8.2.2 Blood Pressure measurements and targets

Patients were initially screened using the Dinamap 1846 SX vital signs monitors (Critikon Inc, Tampa, FL) using an approach previously described (Borrow et al 1982). Eligible patients were enrolled in a wash-out placebo run-in phase of 2 weeks. Thereafter, a 24 hour ambulatory BP monitoring was performed using SpaceLabs 90207 oscillometric monitor (SpaceLabs Inc, Redmond, WA), programmed to obtain readings every 15 minutes from 06H00 to 18H00 and every 20 minutes from 18H00 to 06H00 (O'Brien et al 1991). If the mean daytime ambulatory diastolic BP was ≥90 mm Hg and ≤114 mm Hg, patients were randomized to one of two treatment arms: indapamide SR 1.5 mg once daily (Natrilix SR, Servier Lab), or amlodipine 5 mg once daily (Norvasc, Pfizer). Patients were excluded if their compliance during the placebo run-in phase was poor (<80% or >120% of the expected tablet count). Throughout the study conventional BP was measured according to the American Heart Association guidelines (Frohlich et al 1998).

After one month of therapy, if the BP target was not achieved (daytime ambulatory diastolic BP ≥ 85 mm Hg), perindopril 4 mg o/d (Coversyl, Servier Lab) was added to the diuretic treated group or amlodipine was increased to 10 mg in the CCB treated group. Thereafter, patients continued on the same therapy for a further 5 months with visits at monthly intervals. After 2 months if a mean daytime diastolic ambulatory BP of less 100 mm Hg and a decrease in the mean daytime diastolic ambulatory BP ≥ 10 mm Hg were not achieved, the patients were withdrawn from the study. Throughout the study patients that experienced any serious adverse events or had a daytime systolic ambulatory BP > 180 mm Hg and a daytime ambulatory diastolic BP> 110 mm Hg were also withdrawn.

8.2.3 Echocardiography

Two-dimensional targeted M-mode echocardiograms were obtained as described in chapter 2 with a Hewlett Packard Sonos 2500 system using a 2.5 MHz transducer at the end of the two-week washout phase, and after 2 and 6 months of therapy. The echocardiograms were analyzed according to the American Society of Echocardiography recommendations (Sahn et al 1978). Left ventricular mass was derived according to an anatomically validated regression method that corrects LVM estimates obtained from the recommended measurements (Devereux et al 1986). Left ventricular mass was indexed to body surface area to ensure that blood pressure, rather than adiposity-induced effects were noted. Replicated measurements of LVMI showed that the inter- and intra-observer coefficients of variation were 12.4% and 11.4% respectively.

Statistical analysis

Database management and statistical analysis were performed with SAS software, version 8.2 (SAS Institute Inc, Cary, NC). Between and within-group differences in continuous measurements were tested with multiple repeated measurements analysis of variance, adjusting for baseline BP values. Proportions were compared using the Chi square test or Fisher exact when necessary.

8.3 Results

Of the 283 patients screened for the study, 125 were randomized, 61 patients received amlodipine 5 mg/once daily (od) and 64 patients received indapamide SR 1.5 mg o/d as initial treatment. The baseline study groups were mostly female with a high mean body mass index (BMI) (Table 8.1). There were no statistical differences between

Table 8.1. Baseline demographic characteristics of the study groups

	Amlodipine (n=61)	Indapamide SR (n=64)
Gender (n/% female)	43 (71)	42 (66)
Age (years)	53.7 ± 10.5	51.6 ± 10.7
Body weight (kg)	78.9 ± 14.6	77.8 ± 16.2
Body mass index (kg/m^2)	30.8 ± 6.5	29.9 ± 6.8
Serum K^+ (mmol/l)	3.7 ± 0.7	3.7 ± 0.9
Serum glucose (mmol/l)	5.1 ± 1.6	5.3 ± 2.7
Total cholesterol (mmol/l)	5.1 ± 1.0	5.2 ± 1.2
Serum creatinine (µmol/l)	80 ± 18	84 ± 18
Blood Pressure		
Conventional SBP/DBP (mm Hg)	151 ± 16 / 94 ± 8	153 ± 14 / 95 ± 8
Heart rate (beats/min)	74 ± 10	74 ± 11
24 hour ambulatory SBP/DBP (mm Hg)	148 ± 14 / 94 ± 6	148 ± 12 / 95 ± 6
Daytime SBP/DBP (mm Hg)	152 ± 13 / 99 ± 5	153 ± 12 / 101 ± 6*
Night-time SBP/DBP (mm Hg)	144 ± 16 / 89 ± 7	143 ± 15 / 90 ± 8

SBP, systolic blood pressure; DBP, diastolic blood pressure. * p =0.03 for daytime diastolic BP between the two groups.

baseline characteristics, except for the daytime diastolic ambulatory BP between the two groups (Table 8.1). From the cohort, 44 patients in the amlodipine treated group and 42 patients in the indapamide SR treated group completed 6 months of treatment. Thirteen patients were withdrawn and 4 defaulted in the amlodipine treated group and 17 were withdrawn, and 5 patients defaulted in the indapamide SR treated group. Major adverse events requiring withdrawal were: angioneurotic oedema (1 patient) due to perindopril, severe dizziness (1 patient) due to indapamide SR; and pedal oedema (6 patients) and generalized oedema (1 patient).

8.3.1 Blood pressure and heart rate

The reduction in BP at 1 month of therapy was similar in both groups (Table 8.2). The decline in ambulatory daytime SBP/DBP after 1 month of therapy was 14/8 mm Hg in the amlodipine treated group and 15/9 mm Hg in the indapamide SR treated group (Table 8.2). At 1 month BP control rates were similar in both groups. Using a target daytime diastolic ambulatory BP<85 mm Hg, 16% (9/58) and 23% (14/62) control rates were achieved for amlodipine and indapamide SR respectively. The daytime ambulatory systolic BP was <140 mm Hg in 55% (32/58) of patients in the amlodipine treated group and 61% (38/62) of patients in the indapamide SR treated group. The daytime ambulatory systolic and diastolic BP was less than 140/90 mm Hg in 35 % (20/58) of patients in the amlodipine treated group and 42% (26/62) of patients in the indapamide SR treated group.

At both 2 and at 6 months, the decrease in BP and BP values achieved were similar between the groups (Table 8.2). Although the baseline daytime ambulatory diastolic BP was slightly higher in the indapamide SR treated group, at the end of the study, the indapamide SR treated group achieved BP control (daytime ambulatory

Table 8.2. Conventional, Dinamap and ambulatory blood pressures at baseline, 1 month and 6 months of therapy

	Baseline	1 month	6 months
Amlodipine, n=	61	58	44
Conventional SBP/DBP (mm Hg)†	153 ± 15 / 97 ± 8	138 ± 15 / 90 ± 8*	127 ± 13 / 81 ± 8*
Dinamap SBP/DBP (mm Hg)	151 ± 16 / 94 ± 8	136 ± 14 / 87 ± 8*	124 ± 15 / 79 ± 7*
24-hour SBP/DBP (mm Hg)	148 ± 14 / 94 ± 6	134 ± 12 / 86 ± 8*	126 ± 11 / 81 ± 6*
Daytime SBP/DBP (mm Hg)	152 ± 13 / 99 ± 5	138 ± 12 / 91 ± 8*	129 ±11 / 85 ± 5*
Indapamide SR, n=	64	62	42
Conventional SBP/DBP (mm Hg)†	153 ± 14 / 97 ± 7*	135 ± 15 / 88 ± 8*	128 ± 14 / 85 ± 8*
Dinamap SBP/DBP (mm Hg)	153 ± 14 / 95 ±7*	135 ± 18 / 86 ±12*	127 ± 18 / 81 ±10*
24-Hour SBP/DBP (mm Hg)	148 ± 12 / 95 ± 6*	134 ± 15 / 87 ± 9*	126 ± 16 / 81 ± 8*
Daytime SBP/DBP (mm Hg)	153 ± 12 / 101 ±6*	138 ± 15 / 92 ±10*	130 ± 15 / 86 ± 8*
Nighttime SBP/DBP (mm Hg)	143 ± 15 / 90 ± 8*	130 ± 15 / 83 ± 9*	123 ± 17 / 77 ± 9*

SBP/DBP; systolic blood pressure/diastolic blood pressure. * $p < 0.0001$ (between baseline and 1 month / 6 months) † Blood pressure was measured according to the recommendation of the American Heart Association.

diastolic BP<85 mmHg) in 52% of patients (22/42), which was similar to that in the amlodipine treated group, where BP control was achieved in 52% (23/44) of patients. In those patients who remained on initial therapy, in the indapamide SR treated group only 3 (7%) of patients remained controlled and in the amlodipine treated group only 4 (9%) patients remained controlled. After 6 months of therapy the daytime ambulatory systolic BP was less than 140 mm Hg in 86 % (38/44) of patients in the amlodipine treated group and 76% (32/42) of patients in the indapamide SR treated group. The daytime ambulatory systolic and diastolic BP was less than 140/90 mm Hg in 75 % (33/44) of patients in the amlodipine treated group and 67% (28/42) of patients in the indapamide SR treated group. The mean daytime and nighttime heart rate was similar in both groups and did not change significantly throughout the study (data not shown).

8.3.2 Left ventricular mass and remodelling.

The decline in systolic BP was associated with regression of LVMI after 2 and 6 months of therapy (Figure 8.1). This regression was achieved by a reduction in posterior ventricular and inter-ventricular septal wall thickness (PWED, IVS) and not by a decrease in end diastolic diameter (LVEDD) (Table 8.3). Furthermore, a reversal of LV concentric remodelling was noted as evidenced by a reduction in RWT (Figure 8.2). The reduction in LVMI and in RWT was similar in both groups after 2 and 6 months of therapy (Figures 8.1 and 8.2).

8.3.3 Biochemistry

No significant changes in biochemical parameters were noted with treatment except for a similar decrease in cholesterol concentrations in both groups (data not shown) following atorvastatin administration to four patients in the indapamide SR treated

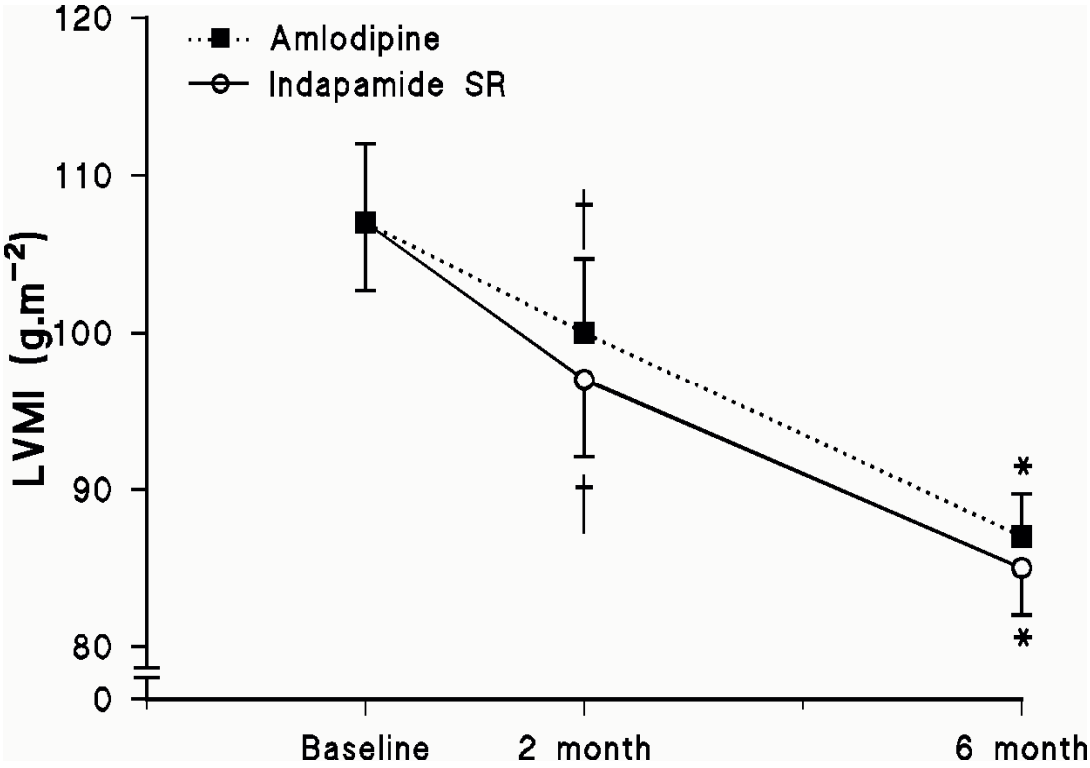


Figure 8.1. Left ventricular mass index reduction after 2 and 6 months of therapy. † p< 0.0001 (2 months versus baseline); * p < 0.001 (6 months versus 2 months).

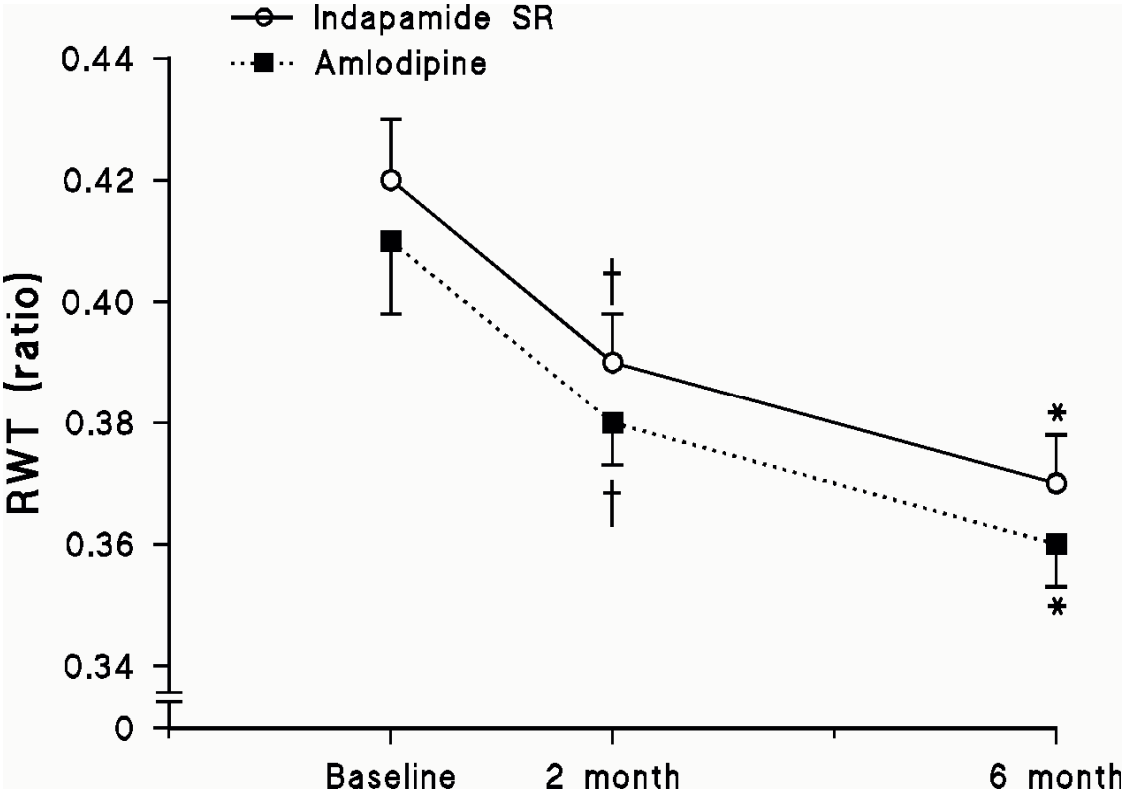


Figure 8.2. Relative wall thickness reduction after 2 and 6 months of therapy. † p< 0.0001 (2 months versus baseline); * p < 0.001 (6 months versus 2 months).

Table 8.3. Echocardiographic data at baseline and after 2 and 6 months of treatment

	Baseline	2 months	6 months
Amlodipine (n=36)			
24-hour SBP/DBP (mm Hg)	147 ± 12/ 93 ± 6	126 ± 9/ 82 ± 5†	125 ± 10/ 80 ± 5
LVEDD (mm)	49.1± 5.2	49.9 ± 4.6	48.8 ± 3.5
PWED (mm)	10.0 ± 1.2	9.4 ± 1.0†	8.7 ± 0.8*
IVSD (mm)	10.5 ± 1.6	9.8 ± 1.3†	9.1 ± 0.9*
LVM (g)	191 ± 54	178 ± 49†	154 ± 27*
Indapamide SR (n=37)			
24 H SBP/DBP (mmHg)	147 ± 13/ 94 ± 6	128 ± 11/ 82 ± 6†	128 ± 16/ 82 ± 9
LVEDD (mm)	49.0 ± 4.3	48.8 ± 4.1	48.4 ± 3.5
PWED (mm)	10.3 ± 1.4	9.5 ± 1.2†	8.9± 1.1*
IVSD (mm)	11.1 ± 1.8	10.0 ± 1.4†	9.4 ± 1.2*
LVM (g)	200 ± 54	176 ± 49†	158 ± 37*

SBP/DBP, systolic blood pressure/diastolic blood pressure

LVEDD, left ventricular end diastolic diameter

PWED, posterior ventricular wall thickness

IVS, inter-ventricular septal wall thickness

LVM, left ventricular mass

*p< 0.001 (2-6 months) † p < 0.0001 (baseline-2 months)

group and to seven patients in the amlodipine treated group. Potassium supplementation was required in two patients in each group.

8.4 DISCUSSION

The major findings of the present study are that in patients of African ancestry with mild-to-moderate hypertension: 1) monotherapy with indapamide SR (1.5 mg o/d) decreases ambulatory and office BP to a similar extent as compared to amlodipine (5 mg o/d) after one month of therapy, 2) the combination of indapamide SR (1.5 mg) and perindopril (4 mg o/d) was equally as effective as amlodipine (10 mg o/d) at lowering BP after 2 and 6 months of therapy and 3) the decline in BP following therapy was associated with continued regression of LVM index and a decrease in RWT to an equivalent extent in both treatment groups.

The present study is the first to compare the efficacy of the sustained release indapamide (thiazide diuretic) to that of the dihydropyridine CCB, amlodipine on ambulatory BP in subjects of African ancestry with mild-to-moderate hypertension. Equivalent efficacy was achieved. This is in contrast to the greater antihypertensive efficacy of CCB (including dihydropyridines) agents as compared to low dose HCTZ (12.5-25 mg daily) used in this ethnic group (Skoularigis et al 1995, Sareli et al 2001). The data in the present study are consistent with the comparable efficacy of indapamide SR 1.5 mg with amlodipine 5 mg at reducing systolic BP in elderly patients of mainly European ancestry with isolated systolic hypertension (Emeriau et al 2001).

In the present study initial monotherapy failed to achieve control of BP to accepted therapeutic targets as determined by ABPM in the majority of patients. Similarly, in the ALLHAT study (The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002) in which 35% of patients were of African ancestry and the initial office BP values in untreated patients in the diuretic (chlorthalidone) and the CCB

(amlodipine) treatment arms were 156/89 mm Hg and 157/90 mm Hg respectively, (as compared to a baseline office BP in the present study of 153/97 mm Hg), although the dose of chlorthalidone was up-titrated to 25 mg daily and the dose of amlodipine was increased to 10 mg daily, 63% of the patients required the addition of a β blocker, atenolol to achieve an office target BP of < 140/90 mm Hg.

In the present study the equivalent effect on BP employing both therapeutic approaches was associated with similar reductions in LVM index and RWT. The significant reduction of RWT in both treatment groups underscores the favorable effect of antihypertensive therapy on LV remodeling.

In summary this study supports the notion that initiating antihypertensive therapy with the diuretic indapamide and then subsequently adding an ACE-I produces similar antihypertensive effects and beneficial effects on LVM as a long-acting CCB in patients of African descent. In conclusion, the results of the present study support the use of indapamide as initial therapy, with an ACE-I added as additional therapy, in hypertensive patients of African ancestry who may require an ACE-I for compelling reasons, such as LVH.

Chapter 9

Conclusions

As reviewed in chapter 1 of the present thesis, it is now well established that LVH is a risk factor for CVD (such as stroke, MI, cardiac death, heart failure etc.) beyond classical cardiovascular risk factors such as conventional BP. Importantly, there is substantial evidence from studies with large sample sizes to suggest that LVM is higher in African-Americans than in European-Americans (Skelton et al 2003, Lorber et al 2003, Kizer et al 2004, Rodriguez et al 2004, Drazner et al 2005) a difference that may translate into a higher prevalence of CVD. However, whether LVM is similarly elevated in groups of African descent living in Africa has not been determined. Consequently, in the initial part of the present thesis (chapter 2) I aimed to establish whether in healthy South Africans of African ancestry, thresholds for LVM are indeed higher than those previously described for studies defining thresholds for LVM in communities of European ancestry.

In chapter 2 of the present thesis, in order to identify the thresholds for LVM in healthy individuals, I first established the most appropriate allometric signals that adjust for growth effects on LVM for the community of African descent living in South Africa that I studied. In 141 healthy individuals obtained from a random sample of nuclear families comprising 399 participants of African ancestry older than 16 years of age and living in metropolitan areas of Johannesburg, I determined that LVM adjusted for body surface area to the first power was an appropriate allometric signal to adjust for growth effects on LVM. The allometric signals that adjust for growth effects on LVM established in other populations considerably overadjusted for LVM in the group that I studied with marked negative relations noted between LVM indexed to height$^{2.7}$ or body surface area$^{1.5}$ and either height or body surface area. I subsequently determined the threshold values for LVM adjusted for body surface area and compared these against data described in other population groups. After adjusting for body surface area to the first power I noted upper thresholds of LVM index of 134 g/m^2 for men and 112 g/m^2 for women in clinically normal individuals in a community of African descent living in South Africa. As compared to

thresholds described for other population samples these thresholds were noted to be only ~10 g/m^2 higher in healthy men of African descent living in South Africa, and only ~5 g/m^2 higher in healthy women of African descent living in South Africa.

24-Hour BP may be more closely associated with LVM than conventional BP, as it reflects BP load over a substantially greater time period. This may be particularly important in groups of African ancestry. Indeed, as compared to European-Americans, African-Americans have an attenuated nocturnal decrease in BP (Profant and Dimsdale 1999, Wang et al 2006). Although data obtained from small studies suggest that this translates into a greater degree of target organ damage in groups of African ancestry (reviewed in chapters 1 and 3), these studies have largely had inconsistent outcomes. No large study has assessed whether ambulatory BP is a better predictor than conventional BP or a predictor independent of conventional BP in groups of African descent. Moreover, whether nocturnal decreases in BP play a substantial role in contributing to LVM in groups of African descent, or whether nocturnal BP is more important that daytime BP in contributing to LVM in groups of African ancestry has not been assessed in large studies with complete ambulatory BP profiles. These questions were addressed in chapter 3 of the present thesis. In this regard, I was able to show that after adjustments were made for sex, age, body mass index, non-independence of family members, antihypertensive treatment, and the presence of diabetes mellitus or an HbA1c>7.0%, neither the ratio of night-to-day BP, nor differences in night-to-day BP were associated with LVM indexed for body surface area. Moreover, after adjustments, conventional, 24-hour, daytime and night-time systolic BP (SBP) were all associated with LVM index, with equivalent relations noted for conventional ($r=0.21$, $p<0.0005$) and 24 hour ($r=0.17$, $p<0.005$) SBP and for daytime ($r=0.17$, $p<0.005$) and night-time ($r=0.16$, $p<0.01$) SBP. Diastolic BP was not independently related to LVM index. With conventional BP included as a covariate, neither 24-hour, daytime nor night-time BP were independently associated with

LVM index in the whole group. However, in sex-specific analysis, night-time BP was associated with LVM index independent of conventional BP in men (n=110, r=0.21, p<0.05). These data therefore provide some evidence to indicate that in persons of African descent, nocturnal BP may predict LVM index beyond conventional BP in men, but not in women. However, an increased sample of men is required to confirm these data.

Left ventricular mass is partly determined by arterial stiffness, which may impact on central rather than peripheral (brachial artery) BP. Arterial stiffness may therefore predict LVM independent of brachial artery BP values. However, as indicated in chapter 4, in this regard the present evidence is controversial. However, arterial stiffness is greater in groups of African as compared to European ancestry (Din-Dzietham et al 2004; Shiburi et al 2006; Chaturvedi et al 2004) and there are no studies evaluating the brachial artery-independent effect of arterial stiffness on LVM in groups of African ancestry. In the present thesis I therefore determined whether the relationship between an index of arterial stiffness (pulse wave velocity [PWV]) or wave reflection (augmentation index [AI]) and LVM is independent of conventional BP in randomly recruited subjects of African ancestry (chapter 4). Applanation tonometry was performed at the carotid, radial and femoral arteries and central AI and aortic PWV (carotid-femoral) derived from these measures. LVM indexed for body surface area was determined using echocardiography. Univariate analysis demonstrated a relationship between PWV and LVM index (r=0.28, p<0.0001) and between AIc and LVM index (r=0.19, p<0.001), but on sex-specific analysis, the relationship between PWV and LVM index was present in women (r=0.49, p<0.0001), but not in men (r=0.06, p=0.54), whereas the relationship between AIc and LVM index was noted in both gender groups. After adjusting for body mass index, antihypertensive treatment, the presence or absence of diabetes mellitus or abnormal blood glucose control (HbA1c), non-independence of family members and either conventional systolic BP or pulse pressure, PWV (r=0.25, p<0.0005), but not AIc (p=0.40-

0.86) was independently associated with LVM index in females. In males, neither PWV nor AIc were associated with LVM index independent of conventional BP and other confounders. These data therefore suggest that PWV may refine the ability to predict LVM index beyond conventional BP in groups of African descent, but this effect is sex-specific being limited to females only.

As reviewed in chapter 1, a reduction of LVM is established as a desirable therapeutic goal in hypertension. However, there is substantial controversy as to whether conventional BP or ambulatory BP measurements should be used to assess changes in LVM index with antihypertensive therapy. Studies that have assessed this question have been conducted exclusively in groups of European descent. However, as groups of African descent have an attenuated nocturnal decline in BP (Profant and Dimsdale 1999, Wang et al 2006) and antihypertensive-induced decreases in LVM may therefore depend more on changes in ambulatory rather than conventional BP in this ethnic group. In the present thesis, I explored the extent to which changes in conventional and ambulatory BP predict regression of LVM index in response to antihypertensive treatment in previously untreated and treated patients of African ancestry with sustained hypertension (chapter 5). In this study 173 patients who, off treatment, had a daytime diastolic BP ranging from 90 to 114 mm Hg were enrolled. Antihypertensive drugs were titrated and combined to reduce the daytime diastolic BP below 90 mm Hg. Echocardiograms were obtained at baseline and follow-up. Mean systolic/diastolic clinic BP, 24-hour BP, and LVM index were similar in previously untreated (n=64) and previously treated (n=109) patients and averaged 171/102 mm Hg, 151/97 mm Hg, and 118 g/m^2, respectively. At 4 months, these values had decreased ($p<0.001$) by 26/12 mm Hg, 23/14 mm Hg, and 14 g/m^2 in previously untreated patients and by 22/9 mm Hg, 21/13 mm Hg, and 19 g/m^2 in previously treated patients. In the previously untreated patients, the regression in LVM index correlated to a similar degree ($p<0.09$) with the decreases in the conventional ($r=0.34$; $p<0.005$) and the 24-hour ($r=0.26$; $p<0.04$) systolic BP. In the previously treated

patients, the corresponding correlations were 0.02 ($p<0.82$) and =0.10 ($p<0.32$), respectively. Compared with the 24-hour systolic BP, automated oscillometric measurements of systolic BP obtained at the clinic yielded similar results. These data indicated that in previously untreated patients of African ancestry with sustained hypertension followed at a single center, reductions in clinic and ambulatory systolic pressure in response to antihypertensive treatment equally predicted the regression in LVM index. Despite these conclusions, the limited sample size of untreated hypertensives prevented me from performing sex-specific analysis. Consequently, whether this effect is specific for women, and whether the conventional BP-independent relationship between nocturnal systolic BP and LVM index noted in men as described in chapter 3, translates into a greater importance for ambulatory as compared to conventional BP when predicting treatment-induced changes in LVM index requires further study.

Recent evidence indicates that antihypertensive agents that target the RAS regress LVH more effectively than some other classes of antihypertensive agents, despite similar conventional BP effects (Devereux et al 2004[1], Zanchetti et al 2002). However, in these studies only a relatively small number of patients of African descent were recruited. In a sub-analysis in those patients of African ancestry that were recruited, RAS blockers did not show a BP-independent effect on LVM index (Devereux et al 2004[1]). These data are consistent with small studies conducted in groups of African ancestry in South Africa conducted over relatiovely short periods (reviewed in chapter 1). However, the regression of LVH may only be achieved after 2 years of therapy. Thus, in the reduction of LVM, the relative importance of BP lowering versus the class of antihypertensive employed in groups of African ancestry remains uncertain. In chapter 6 I describe a single-centre, randomized trial where I explored the independent associations between LVM and both ambulatory BP and treatment with an ACE-I over a 25-month follow-up period. Patients of African ancestry (n=185 at enrollment) with a mean daytime diastolic BP ranging from 90-114 mm Hg off-treatment were randomized to receive either enalapril, calcium channel

blockers (nifedipine or slow release verapamil), or hydrochlorothiazide as initial therapy. Doses were increased and additional therapy, including enalapril, added to achieve a target daytime diastolic BP below 90 mm Hg. At 4, 13 and 25 months of therapy 66, 71 and 72 % of patients had BP values within target ranges. LVM index decreased from 118±33 g/m^2 at baseline to 101±25, 101±23, and 96±22 g/m^2 at 4, 13 and 25 months of therapy ($p<0.001$ compared to baseline). Accounting for effects on either ambulatory or conventional BP at each time point, the use of enalapril was associated with neither LVM index, nor with LV relative wall thickness over the treatment period. However, in-treatment systolic conventional and night-time BP were associated with both LVMI (conventional; p= 0.01, night-time; p=0.01) and LV relative wall thickness (conventional; p=0.03, night-time; p=0.005). Although 24 hour and daytime BP were not associated with LVM index, both 24-hour (p=0.005) and daytime (p=0.017) BP were associated with in-treatment LV relative wall thickness. These data indicated that in the treatment of hypertension in groups of African origins, the use of an ACE-I confers no additional benefits on LVM beyond that produced by effects on BP.

As indicated above, although antihypertensive agents that target the RAS produce conventional BP-independent effects on LVM in groups of European ancestry, in hypertensives of African ancestry, this does not appear to be the case. However, groups of African ancestry also have distinct BP responses to antihypertensive agents that target the RAS (Sareli et al 2001, Woodiwiss et al 2006). Moreover, although I was able to demonstrate that the use of an ACE-I produced no appreciable benefit over that of BP changes in mediating a reduction of LVM over a 25-month treatment period, in this study, patients were not selected for the presence of LVH. Whether decreases in BP associated with the use of agents that specifically target the RAS predict regression of LVH in patients of African ancestry is therefore uncertain. In chapter 7 I addressed this question. In this chapter I describe a single-centre study where patients of African ancestry with a mean daytime diastolic ambulatory BP (ABP)$\geq$90 mm Hg and LVH on echocardiography

received candesartan cilexetil 8-16 mg once daily for 2 months followed by the addition of hydrochlorothiazide 12.5 mg daily for a further month and subsequently ramipril 2.5-5 mg daily for another 2 months if diastolic ABP remained>90 mm Hg. The impact of changes in ABP on alterations in LVM index was assessed. Of the 86 patients starting, 47 completed the study. Candesartan monotherapy produced only modest decreases in ABP (from 153±17/95±6 to 151±18/93±7 mm Hg at 2 months, $p<0.05$). The addition of a diuretic resulted in a striking decrease in ABP (to 139±21/87±9 mm Hg at 3 months, $p<0.0001$ versus baseline), an effect that was only partially augmented by the addition of ramipril ($p<0.05$). LVM index decreased from 122±20 to 111±23 g/m^2 ($p<0.005$) with treatment. Adjusting for gender, changes in systolic ABP (daytime, $r=0.46$, $p=0.006$) were predictive of changes in LVM index. These results suggested that in hypertensive patients of African ancestry receiving therapy targeting the RAS and a diuretic agent, changes in systolic BP may be an appropriate surrogate for target organ effects. Clearly the outcomes of this study may have been largely driven by the impact of the diuretic agent on BP. However, diuretic agents at this dose, when used as monotherapy, do not mediate such profound decreases in systolic BP (~12 mm Hg on average in 24-hour systolic BP) in this ethnic group (Skoularigis et al 1995, Sareli et al 2001). Therefore, the impact of antihypertensive therapy on BP and LVM index can only be attributed to combination therapy and thus in-part to RAS blockade.

Although antihypertensive agents that target the RAS have a limited efficacy when used as monotherapy in patients of African ancestry (Sareli et al 2001, Woodiwiss et al 2006, chapter 7), there are compelling indications for their use, including the presence of LVH (Hypertension Society of Southern Africa, [Seedat et al 2006], The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2003). Although when used alone RAS blockers have little antihypertensive efficacy in many patients of African descent, when used together with a diuretic agent, the synergy between these two classes of agents enhances the effects of either class used alone.

However, in the treatment of hypertension in subjects of African origins, there is question as to whether diuretic therapy, followed by the addition of an ACE-I is as effective as calcium channel blockers on BP and LVM. In chapter 8 I have described a study where I compared the effects of slow release (SR) indapamide (diuretic agent) with the addition of an ACE-I to that of the calcium channel blocker, amlodipine, when used as initial therapy, on BP and LVM over 6 months of treatment in patients of African descent. Patients with mean daytime ambulatory diastolic BP (DADBP) ≥90 mm Hg and ≤110 mm Hg (n=125, age 53 $\pm$ 11, 68% female) were randomized to receive open-label indapamide SR 1.5 mg or amlodipine 5 mg. If DADBP at 1 month was ≥ 90 mm Hg, perindopril 4 mg was added to indapamide SR or the dose of amlodipine was increased to 10 mg. After 1 month, there was an equivalent decline in systolic and diastolic BP in the two groups ($p<0.0001$). In the indapamide SR treated group (n=62) the daytime BP decreased from 153±12/101±6 to 138±15/92±10 mm Hg and in the amlodipine treated group (n=58) it decreased from 152±13/99±5 to 138±12/91±8 mm Hg. At 6 months DABP decreased to 130±15/86±8 and to 129±11/85±5 mm Hg for the indapamide SR (n=42) and amlodipine (n=44) treated groups respectively. Both groups showed equivalent regression in LVM index. These data suggest that in hypertensive patients of African ancestry initiating therapy with the diuretic, indapamide SR and then adding the ACE-I, perindopril 4 mg, is equally as effective as amlodipine (calcium channel blocker) therapy at reducing BP and modifying target organ changes.

The individual studies described in the present thesis have a number of limitations all of which have been acknowledged in the “discussion” section of the relevant chapters, and hence will not be elaborated on again. However, in addition, overall the present thesis is limited by the absence of additional studies or analyses that are presently still being conducted and go beyond the scope of the present thesis. First, I was unable to account for a large portion of the variability in LVM in the cross-sectional studies performed. Additional factors that may account for a considerable portion of the variability

of LVM in the population studied could include synergy as opposed to just additive effects between adiposity and BP; as well as an impact of genetic factors. Presently, the cross-sectional study performed on nuclear families is under-sized to perform intrafamilial aggregation analysis on LVM index. Once this study is sufficiently powered to perform these analyses they will be conducted. Second, a prospective, intervention-based study assessing whether arterial stiffness changes are able to predict the regression of LVH independent of conventional BP is outstanding. This study is presently being planned and will be conducted once we have an understanding of the conventional BP-independent impact of arterial stiffness on other target organ changes, including urinary albumin-to-creatinine ratios.

Thus, in conclusion, the present thesis contributes to our knowledge of LVM in groups of African descent living in Africa in the following way. First, I have been able to demonstrate the appropriate allometric signals that adjust for growth effects on LVM in this group and that growth signal signals for other populations are inappropriate for the present population. Second, in groups of African ancestry living in Africa, nocturnal BP appears to have a conventional BP-independent effect on LVM in men, but not in women, but this requires confirmation in a larger group of men. In contrast, in this same population group, arterial stiffness appears to have a conventional BP-independent effect on LVM in women, but not in men. Third, in this population, reductions in LVM produced by antihypertensive therapy appear to be equally as closely related to conventional as ambulatory BP, but further studies are required in men. Fourth, in contrast to findings in groups of European ancestry, where RAS blockers produce unique benefits on LVM beyond conventional BP reductions, in groups of African ancestry in Africa, RAS blockers produce no BP-independent effects on reductions in LVM. Moreover, in this population, decreases in LVM in patients with LVH produced by RAS blockers are related to BP changes. Last, despite the ineffectiveness of RAS blockers on BP when used as monotherapy, RAS blockers together with diuretics are equally as efficacious in

decreasing BP and LVM as compared to a class of antihypertensive agents with established efficacy in this population (calcium channel blockers). Hence when compelling indications for RAS blockade exist, RAS blocker-diuretic combinations are effective therapy in patients of African descent living in Africa.

APPENDIX 1

Formulae for left ventricular (LVM) mass derived from echocardiography measurements.

1). LV mass calculated according to the American Society of echocardiography convention without adjustments for potential over-corrections.

$$LVM = 0.8 \times [1.04 (LVEDD + IVS + PWT)^3 - (LVEDD)^3]$$

where LVEDD = LV internal diameter, IVS =LV septal thickness, PWT = posterior wall thickness, all measured at diastole in centimeters.

2. LV mass calculated according to the American Society of echocardiography convention with the Devereux correction adjusting for over-corrections.

$$LVM = 0.8 \times [1.04 (LVEDD + IVS + PWT)^3 - (LVEDD)^3] + 0.6g$$

3. LV mass calculated according to the Penn Method

$$LVM = [1.04 (LVEDD + IVS + PWT)^3 - (LVEDD)^3] - 13.6g$$

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