LEFT VENTRICULAR HYPERTROPHY AND ITS DETECTION IN AN AFRICAN COMMUNITY

FABIAN MAUNGANIDZE

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ABSTRACT

Left ventricular hypertrophy (LVH), the detection of which is recommended for routine risk prediction by all guidelines, is more prevalent in groups of African ancestry. This is in-part attributed to higher prevalence rates of obesity. The ability to detect LVH using electrocardiographic (ECG) criteria may be modified in groups of African ancestry. The impact of co-existent obesity on the ability to detect ECG-LVH in this ethnic group has not been determined. Moreover, whether estimated glomerular filtration rate (eGFR) or serum C-reactive protein (CRP concentrations are independently associated with LV mass index (LVMI) and can therefore be used to complement ECG criteria for LVH detection is uncertain.

ECG voltage criteria for the detection of echocardiographic LVH were evaluated in 661 participants from a community sample of African ancestry (43% obese). Body mass index (BMI) was inversely associated with Sokolow-Lyon (SL) voltages (partial r=-0.27, p<0.0001) and no BMI-Cornell voltage relations were noted (p=0.21). BMI was associated with voltage criteria that incorporate only limb lead recordings (r=0.17-0.23), but these relationships were weaker than BMI-LVMI relations (r=0.36, p<0.01-p<0.0001 for comparisons of r values). All ECG criteria were as strongly related to blood pressure (BP) as LVMI. Sokolow-Lyon voltage-LVMI relations were noted only after adjustments for BMI (p<0.02) and SL voltages showed no performance for LVH detection. Cornell voltages showed significant performance in the non-obese (area under the receiver operating curve [AUC]=0.67±0.04, p<0.0005), but not the obese (AUC=0.56±0.04, p=0.08). ECG criteria which employ limb-lead recordings only (e.g. RaVL) showed better performance in non-obese than obese (AUC=0.75±0.04 and 0.59±0.04 respectively, p<0.005 for comparison) and markedly reduced specificity for LVH detection in obese (76%) than non-obese (92%, p<0.0001) despite similar sensitivities (32 vs 29%). Thus, in groups of African ancestry, obesity contributes toward a poor validity and performance of all voltage criteria for the detection of LVH. None of the current criteria are recommended for use in

obesity in groups of African descent. Alternative approaches are required for LVH detection in these groups.

In 621 randomly selected participants from the community sample [332 were normotensive (NT)], eGFR was associated with LVMI and LVM in excess of that predicted from stroke work (inappropriate LVM, LVM_{inappr}) in all participants (LVMI: partial r=-0.18, p<0.0001; LVM_{inappr}: partial r=-0.17, p<0.0001) and NT (LVMI: partial r=-0.23, p<0.0001; LVM_{inappr}: partial r=-0.22, p<0.0001) separate from hypertensives. When replacing clinic BP with either aortic systolic BP (applanation tonometry and SphygmoCor software), 24-hour BP, aortic pulse wave velocity (PWV) (applanation tonometry and SphygmoCor software), stroke work (for LVMI), LV end diastolic diameter (LVEDD), or circumferential wall stress in the regression models, eGFR retained strong associations with LVMI (p=0.01 to <0.0001) and LVM_{inappr} (p<0.005 to <0.0001). Thus, strong relationships between eGFR and LVM occur at a community level irrespective of the presence of hypertension and independent of 24-hour and aortic BP, PWV, LVEDD, stroke work and wall stress. The independent relationships between eGFR and LVMI, support the notion that eGFR may be evaluated for LVH detection.

In 361 randomly selected participants from a community with a high prevalence of CRP concentrations considered to be high-risk (54.0%), but without cardiovascular or renal disease, serum CRP concentrations were correlated with both LVMI and LVM_{inappr} (p<0.0001). With adjustments for a number of potential confounders including age, systolic BP, waist circumference (or BMI), and glucose control (glycated haemoglobin), the relationships between serum CRP concentrations and both LVMI and LVM_{inappr} (partial r=0.11, p<0.05 for both) persisted. The independent relationship between CRP and LVMI or LVM_{inappr} translated into a higher multivariate-adjusted LVMI and LVM_{inappr} values in the highest as compared to the lowest quartile of CRP (LVMI; highest quartile CRP=48.8±10.7, lowest quartile CRP=45.0±11, p<0.05; LVM_{inappr}; highest quartile CRP=137±24, lowest quartile CRP=127±24, p<0.05). The independent relationships

between CRP and LVMI, support the notion that CRP may also be evaluated for LVH detection.

In 358 participants from a randomly selected community sample with a high prevalence of obesity (41%), a combination of CRP concentrations and eGFR above or below the median for the sample respectively showed significant performance (AUC=0.61±0.03, p<0.0005), but a low specificity for LVH detection (77%). When eGFR and CRP concentrations were employed to complement RaVL, although the overall performance did not improve (AUC=0.71±0.03, p<0.0005, RaVL alone: AUC=0.70±0.03), the specificity increased (93%) whilst sensitivity (25%) was in-line with previously reported sensitivities for LVH detection using ECG criteria in alternative population samples. Without changing overall performance, eGFR together with RaVL increased the specificity to 88% and CRP concentrations when considered together with RaVL increased the specificity to 87%. Thus, in a community sample where the specificity and performance of ECG criteria for LVH detection are poor, the use of eGFR and/or CRP concentrations to complement ECG criteria increase the specificity without altering the overall performance.

In conclusion, the present thesis provides evidence to indicate that current ECG criteria for the detection of LVH are invalid in obese individuals of African ancestry, but that clinical markers of renal dysfunction and systemic inflammation, which are associated with LVMI independent of haemodynamic factors and co-morbidities may be employed to complement ECG criteria to improve the specificity for LVH detection.

DECLARATION

I, **Fabian Maunganidze** declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……
FABIAN MAUNGANIDZE

This **5th** day of **September 2013**

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 approval numbers are M020472 (renewed as M070469 and M1204108) and M10345.

……
FABIAN MAUNGANIDZE

This **5th** day of **September 2013**

…… ……

Prof. Angela Woodiwiss (supervisor 1) Prof. Gavin Norton (supervisor 2)

Date: …… Date: ……

Dedicated to my late brother

RICHARD TONDERAI MAWUNGANIDZE

(aka senior) who inspired me to learn and to aim high

and to my children

TAPIWA, MUFARO, ANOGONAISHE AND NOKUTENDA

who always see me as a superstar.

PUBLICATIONS AND CONFERENCE PRESENTATIONS

In support of the present thesis, the work described herein has been published in the *Journal of Hypertension* as indicated below or manuscripts are currently being written for submission to a reputable journal. In addition the conferences and the work presented at these conferences, which form part of my thesis, are also listed.

PUBLICATIONS

a) Fabian Maunganidze, Gavin R. Norton, Muzi Maseko, Carlos Libhaber, Olebogeng H. Majane, Angela J. Woodiwiss. Obesity Markedly Attenuates the Validity and Performance of All Electrocardiographic Criteria for Left Ventricular Hypertrophy Detection in a Group of African Ancestry. *J Hypertens* 2013;31:377-383.

b) Fabian Maunganidze, Gavin R Norton, Muzi J Maseko, Carlos D Libhaber, Olebogeng HI Majane, Pinhas Sareli, Angela J Woodiwiss. Relationship between glomerular dysfunction and left-ventricular mass independent of haemodynamic factors in a community sample. *J Hypertens* 2013;31:568-575.

CONFERENCE PRESENTATIONS

1) International Union of Physiological Sciences (IUPS) 2013 Congress: 21 – 26 July 2013 (*The International Convention Centre, Birmingham, United Kingdom*)
   Poster Presentation – "*Relationship Between Chronic Kidney Disease and Left Ventricular Mass Independent of Haemodynamic Factors in an African Community Sample."*

2) Wits Faculty of Health Sciences Research Day and Post Graduate Expo: 19 September 2012 (*University of the Witwatersrand, Johannesburg, South Africa*)

Oral Presentation – "*Obesity Effects on the Usefulness of Electrocardiographic Criteria for Left Ventricular Hypertrophy Detection in a Group of African Ancestry*"

3) Physiology Society of Southern Africa (PSSA) 39th Annual Conference: 10 – 13 September 2012 (*University of Stellenbosch, Stellenbosch, South Africa*)

Oral Presentation – "*Obesity Effects on the Usefulness of Electrocardiographic Criteria for Left Ventricular Hypertrophy Detection in a Group of African Ancestry*"

4) Association of African Physiological Sciences (AAPS) 6th Congress: 2 – 5 September 2012 (*Suez Canal University, Ismailia, Egypt*)

Poster Presentation – "*Effects of Obesity on the Reliability of Electrocardiographic Criteria for Left Ventricular Hypertrophy in a Predominantly Obese African Population"*

5) 17th Biennial Congress of the Southern Africa Hypertension Society (SAHS): 3 – 5 March 2012 (*Southern Sun Cape Sun, Cape Town, South Africa*)

Oral Presentation – "*Electrocardiographic Criteria for Left Ventricular Hypertrophy in a Predominantly Obese African Population with a high prevalence of hypertension"*

6) Physiology Society of Southern Africa (PSSA) 39th Annual Conference: 28 – 31 August 2011 (*University of the Western Cape, Cape Town, South Africa*)

Oral Presentation – PhD research findings on the "*The Most Reliable Electrocardiographic Criteria for Left Ventricular Hypertrophy in a Predominantly Obese African Population"*

7) The International Conference on Prehypertension and Cardio Metabolic Syndrome: 24 - 27 February 2011 (*The Hilton Vienna Hotel, Vienna, Austria*)

E-Poster Presentation - Presented my updated research findings on the "*Validity of Electrocardiographic Criteria for Left Ventricular Hypertrophy in a Population Sample of African Ancestry*"

8) Physiology Society of Southern Africa (PSSA) 38th Annual Conference – 27 - 29 September 2010 (*East London, South Africa*)

Oral Presentation - Presented my preliminary research findings on the "*Validity of Electrocardiographic Criteria for Left Ventricular Hypertrophy in a Population Sample of African Ancestry*"

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LIST OF ABREVIATIONS

12L	12 Lead QRS Sum
3D Echo	Three-Dimensional Echocardiography
AA	African American
ACEI	Angiotensin Converting Enzyme Inhibitor
Afr	African
AIx	Augmentation Index
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AP	Augmentation Pressure
APSIS	Angina Prognosis Study in Stockholm
ARIC	Atherosclerosis Risk in Communities
AST	Aspartate Transaminase
AUC	Area Under the Receiver Operating Curve
BIRNH	Belgian Inter-University Research on Nutrition and Health
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BSA	Body Surface Area
CAD	Coronary Artery Disease
CARDIA	Coronary Artery Risk Development in Young Adults
CASTEL	Cardiovascular Study in the Elderly
Cau	Caucasian
CHF	Congestive Heart Failure
CHS	Charleston Heart Study
Circ	Circumference

CKD	Chronic Kidney Disease
CNPr	Cornell Product
CNV	Cornell Voltage
Creat	Creatinine
CRI	Chronic Renal Impairment
CRP	C-reactive protein
CTV	Composite Time Voltage
CV	Cardiovascular
CVA	Cerebrovascular Accidents
CVD	Cardiovascular Disease
CVIP	Cardiovascular Irbesartan Project
DBP	Diastolic Blood Pressure
DHCCP	Department of Health and Social Security Hypertension Care Computer Project
DM	Diabetes Mellitus
Dp	Diastolic Pressure
ECG	Electrocardiogram/ Electrocardiography/ Electrocardiographic
Echo	Echocardiography/ Echocardiographic
EDD	End Diastolic Diameter
EDV	End Diastolic Volume
eGFR	Estimated Glomerular Function Rate
ESRD	End Stage Renal Disease
ESV	End Systolic Volume
GFR	Glomerular Function Rate
GGT	Gamma Glutamyl Transferase
Gub-Ung	Gubner-Ungerleider
GUPr	Gubner Ungerleider Product
GUV	Gubner Ungerleider Voltage

HbA1c	Glycated Haemoglobin
HD	Haemodialysis
HDL	High Density Lipoprotein
HEART	Hypertrophy at ECG And its Regression during Treatment
HHANES	HISPANIC Health and Nutrition Examination Survey
Hisp	Hispanic
HOPE	Heart Outcomes Prevention Evaluation
hr	Hour
Hs-CRP	High Sensitivity C-reactive Protein
HT	Hypertensive
HTN	Hypertension
HYPERGEN	Hypertension Genetic Epidemiology Network
IVST	Interventricular Septal Wall Thickness
LAVI	Left Atrial Volume Index
LBBB	Left Branch Bundle Block
LDL	Low Density Lipoprotein
LDL-chol	Low Density Lipoprotein Cholesterol
LEOGRA	Last Evidences of Genetic Risk factors in the Aged
LIFE	Losartan Intervention For Endpoint Reduction in Hypertension
LN	Lupus Nephritis
LV	Left Ventricle/ Left ventriclar
LVEDD	Left Ventricular End Diastolic Diameter
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End Systolic Diameter
LVESV	Left Ventricular End Systolic Volume
LVH	Left Ventricular Hypertrophy
LVIDs	Left Ventricular Internal Diameter in Systole

LVM	Left Ventricular Mass
LVMI	Left Ventricular Mass Index
LVM_{inappr}	Inappropriate Left Ventricular Mass
MA	Microalbuminuria
MAGICS	Microalbuminuria: Genoa Investigation on Complications Study
MAP	Mean Arterial Pressure
MDRD	Modification of Diet in Renal Disease
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial Infarction
MP	Mean Arterial Pressure
MRFIT	Multiple Risk Factor Intervention Trial
MRI	Magnetic Resonance Imaging
Mul	Mulatto ethnicity
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHLS	National Health Laboratory Systems
NOMAS	Northern Manhattan Study
ns/NS	Non significant
NT	Normotensive
PC	Phosphocholine
PD	Peritoneal Dialysis
PIUMA	Progeto Ipertensione Umbria Monitoraggio Ambulatoriale
PP	Pulse Pressure
PWT	Posterior Wall Thickness
PWTs	Posterior Wall Thickness in Systole
PWV	Pulse Wave Velocity
RaVL	R wave in lead aVL
REDHY	Renal Dysfunction in Hypertension

REVE-2	Remodelage Ventriculaire - 2
ROC	Receiver Operating Characteristics
ROMICAT	Rule Out Myocardial Infarction Using Computer Assisted Tomography
RWT	Relative Wall Thickness
SAMPLE	Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEM	Standard Error of the Mean
SL	Sokolow-Lyon
SLPr	Sokolow – Lyon Product
SLV	Sokolow – Lyon Voltage
SOWETO	South Western Township
Sp	Systolic Pressure
TG	Triglyceride
TOD	Target Organ Damage
TPR	Total Peripheral Resistance
UACR	Urinary Albumin –Creatinine Ratio
UAE	Urinary Albumin Excretion
VALIANT	The VALsartan In Acute myocardial iNfarcTion
WC	Waist Circumference

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PREFACE

The growing burden of cardiovascular disease throughout the world, including in Africa, where the dominant populations are of black African ancestry, is a major cause for concern. One approach of refining the ability to predict the risk for cardiovascular events is to detect the presence of an increased left ventricular mass (left ventricular hypertrophy, or LVH). In this regard, groups of black African ancestry may be at a greater risk of cardiovascular disease than other ethnic groups because of a greater prevalence of LVH. Hence, it may be particularly important to detect LVH in this ethnic group. However, the most appropriate method for LVH detection in this ethnic group is uncertain.

Although electrocardiography (ECG) is a simple, cheap and rapid method of detecting LVH, the ability to identify LVH using ECG criteria may be altered in groups of African ancestry. Moreover, obesity, which is becoming increasingly prevalent in this ethnic group, may modify the ability to detect ECG LVH using some criteria. However, the extent to which obesity modifies the ability to employ current ECG criteria for LVH detection in groups of African ancestry is uncertain. This uncertainty prompted me in the present thesis to first evaluate the impact of obesity on the current ECG criteria for LVH detectiion and subsequently examine their performance, sensitivity and specificity in a group of black African ancestry.

As in the present thesis I noted that obesity eliminated the ability of ECG criteria to detect LVH with any degree of precision, I therefore further explored the factors which may be measured clinically to identify those obese patients in whom alternative approaches are required to complement ECG criteria for LVH detection. In this regard, I assessed the possibility that decreases in glomerular filtration rate, as determined from routine clinical assessments, and also whether obesity-related increases in an inflammatory marker commonly measured in clinical practise, are independently related to LV mass. These studies were performed to evaluate whether changes in these values

may be employed to alert observers to the possibility that LVH may exist and hence that echocardiography should be performed to confirm the presence of LVH.

The present thesis is divided into a number of semi-independent chapters, each with sections that include introduction, methods, results and discussion. The first chapter highlights the current knowledge, understanding and controversies on LVH and its detection, leading the reader through the arguments and knowledge gaps that prompted me to perform the studies conducted in the present thesis. The various chapters in this thesis culminate in a summary chapter which summarises the novel findings and consolidates the different findings of each of the individual chapters. Most of the data in this thesis (Chapters 2, 3 and 4) has been peer-reviewed and either published or is in-press in the *Journal Hypertension*. (Maunganidze et al 2013a and Maunganidze et al 2013b) Although the data in Chapters 5 and 6 have not as yet been peer-reviewed, it is currently in preparation for submission to reputable international journals.

CHAPTER 1

Current Understanding and Existing Controversies on Left Ventricular Hypertrophy and its Detection in African Populations.

1.1 Introduction

"Cardiovascular disease" (CVD) is a term that broadly encompasses a number of disorders many of which share a similar aetiology. In this regard, CVD includes disorders of the cerebral vasculature (strokes or cerebrovascular accidents [CVA] and transient ischaemic attacks); coronary arteries (coronary artery disease [CAD] which presents clinically as angina pectoris or myocardial infarction [MI]); endocardium, myocardium or pericardium resulting in congestive heart failure [CHF] or cardiac arrhythmias; kidneys resulting in renal failure; and the peripheral vasculature resulting in peripheral vascular disease. Cardiovascular disease is the leading cause of morbidity and mortality in developed countries and is now considered a major cause of death and disability in developing countries (Pearson 1999, Kahn et al 2000, Yusuf et al 2001, Ebrahim and Smith 2001, Reddy 2002, Boutayeb 2006). It is therefore important to prevent CVD through primary prevention programmes which can effectively detect those at risk. In this regard, there is substantial evidence in favour of the assessment of a number of risk factors for CVD including age, male gender or postmenopausal status, blood pressure (BP), blood cholesterol concentrations, smoking, and diabetes mellitus for routine risk prediction. This has led to the concept of prevention programmes targeting overall risk (global risk) attributed to these traditional risk factors.

While the use of global traditional risk factor assessment was a conceptual advance with proven clinical utility, traditional risk factors were noted to account for less than half the risk of cardiovascular events (Gordon et al 1974) and some epidemiological studies have shown that traditional risk factors do not account for changes in cardiovascular mortality across socio-economic groups (Harald et al 2008). In contrast however, other studies have shown that there is a very good correlation between these risk factors and cardiovascular events (Menotti et al 2009). Nevertheless, patients on adequate treatment for recognised risk factors still experience adverse cardiovascular

events (Kohro et al 2008, Szecsenyi et al 2008). Hence, risk factor assessment with traditional approaches alone may not be ideal.

An important advance in risk factor assessment has been the principle that prior to the development of a cardiovascular event, cardiovascular target organ damage may be detected using a variety of approaches and that the presence of organ damage alerts caregivers to the presence of a higher category of risk. The hypothesis in this regard is that traditional risk factor assessment does not account for temporal and combined effects of risk factors on the cardiovascular system. By assessing organ damage however, one may evaluate an accrual of effects of risk factors over time. This concept has evolved to the point that current guidelines recognise the identification of organ damage as part of usual risk prediction. A number of measures of target organ damage have been shown to predict cardiovascular outcomes beyond traditional cardiovascular risk factors and these include electrocardiographic (ECG) or echocardiographic evidence of left ventricular hypertrophy (LVH) as elaborated in the following sections.

1.1.1 The detection of left ventricular hypertrophy predicts the risk for cardiovascular disease

There are many studies that support the notion that ECG or echocardiographic detection of LVH is a predictor of CVD independent of conventional cardiovascular risk factors, including BP, dyslipidaemia, diabetes mellitus and smoking (Heyden et al 1985, Casale et al 1986, Levy et al 1990a, Koren et al 1991, Ghali et al 1992, Levy et al 1994, Verdecchia et al 1996, Gardin et al 2001, Verdecchia et al 2001, Mathew et al 2001, de Simone et al 2001, Okin et al 2004a, Devereux et al 2004, de Simone et al 2008). Moreover, LVH is a precursor to cardiac dysfunction and arrhythmias (Vasan and Levy 1996, Drazner et al 2004). Whilst earlier prospective studies provide sound evidence to support the detection of LVH for risk prediction (Casale et al 1986, Levy et al 1990a,

Koren et al 1991, Ghali et al 1992, Verdecchia et al 1996), more recent prospective studies, conducted with lower BP targets and in an era of more modern antihypertensive agents, have confirmed the notion that LVH is a strong prognostic predictor (Verdecchia et al 2001, Gardin et al 2001). Clearly if LVH predicts the risk of future CVD, then regression of LVH should be associated with a reduced risk of CVD. One method of reducing left ventricular mass (LVM) and decreasing the prevalence of LVH is through antihypertensive treatment. Older studies have indeed provided evidence to show that regression of LVH with antihypertensive therapy is associated with CVD risk reduction (Levy et al 1994). However, there is also more recent evidence that has been obtained in larger and more carefully conducted studies to support the notion that the impact of BP lowering agents on either ECG-determined LVH or echocardiographically-determined LVM and the associated CVD risk reduction is partly independent of BP changes and other conventional cardiovascular risk factors (Mathew et al 2001, Okin et al 2004a, Devereux et al 2004).

1.1.2 The importance of re-evaluating the diagnostic approach to LVH detection in groups of African ancestry.

As suggested in the aforementioned discussion a variety of methods are currently available for LVH detection in clinical practice. In this regard, it is important to weigh the strengths and weaknesses of each of these appraoches. A comparison of the relative strengths and weaknesses of the different methods available for LVH detection are given in Table 1.1 (Agabiti - Rosei et al 2007). As will be highlighted in subsequent sections (see section 1.2, Chapter 2 and Chapter 3), ECG criteria have a low sensitivity for LVH detection. However, as compared to echocardiography, 3 - dimensional echocardiography, and magnetic resonance imaging (MRI), standard 12-lead electrocardiography is consistently more available, requires less skill and is the cheapest

Table 1.1. Strengths and weaknesses of different methods for the assessment of left ventricular hypertrophy (Agabiti - Rosei *et al* 2007)

	MRI	**3D ECHO**	**ECHO**	**ECG**
Cost	++++	++	++	+
Availability	+	+	+++	++++
Sensitivity	++++	++++	+++	+
Specificity	++++	++++	+++	+++
Reproducibility	++++	++++	+++	++++
Prognostic significance	-	-	++++	++++

ECG, electrocardiography; Echo, echocardiography; 3D Echo, three-dimensional echocardiography; MRI, magnetic resonance imaging. The number of '+' signs indicates the level of the strength and a '-' sign indicates that there is little data to support this feature.

method for LVH detection (Agabiti-Rosei et al 2007, Vanezis and Bhopal 2008). Moreover, as compared to alternative methods of LVH detection, the detection of LVH using ECG criteria has a comparably higher prognostic significance (Agabiti-Rosei et al 2007) and the reproducibility of ECG criteria for LVH detection is high (da Costa et al 2008) (Table 1.1). Thus, ECG criteria for LVH detection have been recommended as the first level of examination in the routine assessment for the detection of cardiovascular abnormalities in the 2007 guidelines of the European Society of Hypertension and European Society of Cardiology (Mancia et al 2007).

In guidelines for the diagnosis and management of hypertension in South African populations, the use of ECG criteria for LVH detection supercede all other methods (Seedat and Rayner 2012). However, as will be described in subsequent discussion, the ability to detect LVH using ECG criteria may be modified in groups of African ancestry (Ashcroft 1972, Munro-Faure et al 1979, Arnett et al 1992, Lee et al 1992, Sutherland et al 1993, Xie et al 1994, Rautaharju et al 1994, Arnett et al 1994, Chaturvedi et al 1994, Arnett et al 1997, Vitelli et al 1998, Chapman et al 1999, Rautaharju et al 2000, Jaggy et al 2000, Okin et al 2002, Spencer et al 2004, Dada et al 2005, Martin et al 2007, Vanezis and Bhopal 2008, Jain et al 2010). In addition, there is evidence to show that some ECG criteria may not be as useful in detecting LVH as others in the presence of obesity (Frank et al 1986, Nath et al 1988, Abergel et al 1996, Okin et al 1996b, Alpert et al 2000, Okin et al 2000, Fraley et al 2005, da Costa et al 2008, Smith et al 2010, Domienik- Karlowicz et al 2011). As obesity is a major cause of LVH (Lauer et al 1991, Schmeider and Messerli 1993, de Simone et al 1994, Gottdiener et al 1994, de Simone et al 1996, Hanevold et al 2004, Chinali et al 2006) and is highly prevalent in groups of African ancestry (Puoane et al 2002, Hanevold et al 2004), the question arises as to the impact of co-existent obesity on the ability to detect ECG-LVH in groups of African ancestry. In this regard, this is a question of considerable public health importance as primary prevention programmes in underdeveloped nations cannot routinely employ echocardiographic or more sophisticated methods for LVH detection. These countries therefore rely on ECG

methods for risk prediction. Hence, in the present thesis I first evaluated the impact of obesity on the validity and performance of ECG criteria for LVH detection in a group of African descent living in Africa. Therefore, in the present chapter I will first describe the current ECG approaches to LVH detection and the evidence to show that the ability to detect LVH using some ECG criteria may be modified by ethnicity and impaired in the presence of obesity (section 1.2). These data will be discussed in the context of the hypothesis developed and evaluated in the current thesis.

In the present thesis I have chosen to refer to all dark-skinned individuals other than those of Meditteranean, Middle-Eastern, South-American, Asian (e.g. Indian), New Zealand (Maori), Australian (Aboriginal), or Pacific Island in origins, and who have known ancestral origins from Africa, as being of African descent or ancestry. For ease of reading in some instances I refer to those dark-skinned persons of African descent or ancestry as Africans. Moreover, where I introduce a geographical distinction between Africans from America (African-Americans; AA), Africans from the Caribbean region (Afro-Caribbeans) and Africans found in any other part of the world (simply referred to as Africans; Afr) it should be noted that this refers to individuals that are assumed to be of similar ethnic origins. Where in the scientific literature ethnic origins were defined as black or white, in this thesis I may refer to these individuals as of African or Caucasian origins respectively.

1.1.3 The importance of assessing the determinants of LVH in groups of African ancestry.

An essential question that warrants consideration is why LVM is able to predict the development of CVD beyond traditional risk factors? Is it possible that the independent relationship between LVH and CVD is not only because LVH indexes a temporal or combined accrual of adverse effects on the cardiovascular system, but also because LVH is caused by adverse changes not accounted for by traditional cardiovascular risk

factors? In this regard, there is now considerable evidence to show that LVH may be accounted for by non-traditional risk factors. This may be particularly important in groups of black African origins who, as will be discussed in section 1.3, appear to have an extraordinarily high prevalence of LVH (Munro-Faure et al 1979, Dunn et al 1983, Arnett et al 1992, Xie et al 1994, Arnett et al 1994, Gardin et al 1995, Kizer et al 2004, Rodriguez et al 2004, Drazner et al 2005, Hanevold et al 2004). As data from the United States of America indicate that 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) and in developing countries in Africa there is some evidence to indicate that stroke is highly prevalent in rural communities (Seedat et al 1998, Kahn and Tollman 1999, Connor et al 2007) and presumably also in urban communities, it is essential that risk prediction in groups of African ancestry is as precise as possible within the confines of existing resources and that appropriate therapeutic strategies are implemented to regress LVH. In this regard, if ECG detection of LVH is suboptimal in groups of African descent, those risk factors for LVH that can be measured with simple and reliable tools could be employed to identify those patients of African descent whom may require referral for echocardiographic LVH detection. Thus, it is important to identify the non-traditional risk factors responsible for the high prevalence of LVH in groups of African ancestry.

The mechanisms of excessive LVH in groups of African descent are uncertain. However, there is a possibility that excessive LVH in this ethnic group may be explained in-part by factors related to obesity or chronic early renal dysfunction, the prevalence rates of which may be high in this ethnic group (Puoane et al 2002, Hanevold et al 2004, Martins et al 2002, Weiner et al 2004, Duru et al 2008). As this ethnic group has a high prevalence of LVH which may in-part be accounted for by the presence of obesity and early renal dysfunction, in the present thesis I evaluated the extent to which one possible factor that is related to obesity (inflammation), and early renal dysfunction may contribute to the development of LVH in a group of African ancestry. Hence in the present chapter I

will also describe the evidence that LVM is particularly high in groups of African ancestry and subsequently outline the evidence in favour or against these non-traditional risk factors accounting for variations in LVM (sections 1.3.1.1 and 1.3.1.2). The inadequacies in this evidence that prompted me to evaluate some of the questions asked in the present thesis will also be underscored. However, before embarking on this discussion, the ECG approach to the detection of LVH and the impact of ethnicity and obesity on these criteria require consideration.

1.2 Electrocardiographic approach to the detection of left ventricular hypertrophy.

Whilst echocardiography allows for visualization of the ventricles, electrocardiography evaluates the cardiac electrical field potentials. Deviations from the expected wave forms and wave amplitudes can be used to predict cardiac abnormalities. However a stronger electrical field does not necessarily correlate directly with an increased LVM (Levy et al 1990b, Bacharova et al 2007a, Bacharova et al 2007b, Vanezis and Bhopal 2008, Bacharova et al 2011). Many of the individual components of the ECG recordings used in the detection of LVH may be related indirectly to LVM as manifestations of conduction abnormalities (Estes and Jackson 2009). Thus, direct extrapolation of ECG amplitudes to LVH diagnosis is difficult. In an attempt in-part to account for this problem, various criteria (formulae) for the diagnosis of LVH have been proposed using ECG recordings and these proposals have been supported by a number of additional studies (Gubner and Ungerleider 1943, Sokolow and Lyon 1949, Holt et al 1969, Romhilt and Estes 1968, Devereux et al 1983, Casale et al 1985, Frank et al 1986, Nath et al 1988, Levy et al 1990b, Molloy et al 1992, Okin et al 1995a, Okin et al 1996a, Abergel et al 1996, Alpert et al 2000, Jaggy et al 2000, Okin et al 2000, Alfakih et al 2004, Bacharova 2007a, Bacharova 2007b, Vanezis and Bhopal 2008, Mazzaro et al 2008, da Costa et al 2008, Calderon et al 2010, Smith et al 2010, Domienik-Karlowicz et al 2011,

Tsiachris et al 2011). In the present thesis I evaluated a range of the most commonly used ECG criteria for LVH detection. These criteria have been summarised in Table 1.2. In section 1.2.1 below, I review the current evidence to support the use of ECG criteria for LVH detection.

Left ventricular hypertrophy has been associated with increased QRS amplitudes, T wave inversion, left axis deviation, ST segment depression, a prolonged QRS duration as well as morphology and amplitude changes of the P waves (Estes and Jackson 2009). These changes may reflect a) a greater charge difference (electrical field potential) generated in the left ventricle during early systole because of the greater bulk of left ventricular tissue and hence and increased amplitude of the QRS complexes; b) repolarisation abnormalities resulting from changes in that part of the ventricle that first repolarises resulting in T-wave inversion; c) secondary conduction defects caused by fibrosis of the myocardium (Banta et al 1964, Estes and Jackson 2009, Bacharova et al 2011) or simply more tissue in an enlarged left ventricle, resulting in left axis deviation (Estes 1966, Estes. and Jackson 2009) and a prolonged QRS complex; and d) subendocardial ischaemia causing S-T segment depression. It has been suggested that LVH leads to a compensatory increase in QRS voltage amplitudes in order to increase ventricular efficiency and strength (Estes and Jackson 2009). Although P wave abnormalities are due to left atrial enlargement, LVH causes left ventricular diastolic dysfunction, an increased strain on the left atrium, and hence left atrial enlargement (Estes and Jackson 2009, Bacharova et al 2011). Thus, P wave abnormalities are considered to reflect the degree of LVH. Hence, ECG criteria for LVH detection may incorporate the use of R and S wave amplitudes, axis deviations, QRS duration, P wave changes and ST segment-T wave changes (Frank et al 1986, Molloy et al 1992, Xie et al 1994, Okin et al 1995a, Okin et al 1996a, Vitelli 1998, Alpert et al 2000, Mazzaro et al 2008, Vanezis and Bhopal 2008, da Costa et al 2008, Estes and Jackson 2009, Jain et al 2010, Bacharova et al 2011).

Table 1.2. Formulae for the common ECG criteria employed for LVH detection

Criteria	**Formula**	**Reference**	**Common abbreviation**
Sokolow-Lyon Voltage (**mV**)	$S_{V1} + R_{V5 \text{ (or V6 if larger)}}$	Sokolow and Lyon 1949	SLV
Sokolow-Lyon Product (**mV x ms**)	Sokolow-Lyon Voltage x QRS duration	Molloy et al 1992	SLPr
Cornell Voltage (**mV**)	$R_{aVL} + S_{V3}$ (+0.8 mV in women)	Casale et al 1985	CNV
Cornell Product (**mV x ms**)	Cornell Voltage x QRS duration	Molloy et al 1992	CNPr
12-lead QRS sum (**mV**)	$QRS_I + QRS_{II}$ …. + QRS_{V6} (i.e. sum of QRS volt age in all 12 leads)	Siegel and Roberts 1982	12L
RaVL voltage (**mV**)	R_{aVL}	Sokolow and Lyon 1949	RaVL
Lewis voltage (**mV**)	$(R_I + S_{III}) – (R_{III}+S_I)$	Lewis 1914	Lew
Gubner-Ungerleider Voltage (**mV**)	$R_I + S_{III}$	Gubner and Ungerleider 1943	GUV
Gubner-Ungerleider Product (**mV x ms**)	Gubner-Ungerleider Voltage x QRS duration	Molloy et al 1992	GUPr

The amplitude of the R or S waves has been employed in most ECG criteria for LVH detection because LVH is strongly associated with increased QRS voltages (Gubner and Ungerleider 1943, Sokolow and Perloff 1961, Estes 1966, Holt et al 1969, Casale et al 1985, Casale et al 1987, Rautaharju et al 1988, Levy et al 1990b, Molloy et al 1992, Okin et al 1995a, Estes and Jackson 2009, Bacharova et al 2011). The identification of alternative criteria however, have additional clinical implications. In this regard, a prolonged QRS duration is strongly and independently associated with LVH (Molloy et al 1992, Okin et al 1995a, Okin et al 1998). The increase in QRS duration is thought to signal a loss of synchrony in left ventricular contraction (Beshai et al 2007, Estes and Jackson 2009) and has a strong association with a high risk of sudden death and ventricular arrhythmias. Nevertheless a prolonged QRS duration has been proposed to be a late phenomenon as with left atrial enlargement (Estes and Jackson 2009). Although an explanation for this relationships has not been forthcoming, T wave changes are strongly associated with diastolic dysfunction (Yu et al 2003, Estes and Jackson 2009, Bacharova et al 2011). In hypertensive patients with LVH, S-T segment depression accompanied by T-wave inversion, often called a strain pattern, independently predicts the onset of congestive heart failure (Okin et al 2006). The poor diagnostic performance of the individual components of the ECG criteria employed to detect LVH has led to the use of combinations of R and S wave amplitudes and this improves the specificity of ECG criteria for LVH detection (Ostrander 1966, Kannel et al 1969, Davis et al 1986, Xie et al 1994) as elaborated on in detail in the following sections (1.2.1 and 1.2.2).

1.2.1. Evidence for the performance of current ECG criteria for LVH detection

Table 1.3 summarises the current evidence to support the use of ECG criteria for LVH detection in Caucasians and in groups of African ancestry. Only those studies with a minimum sample size of 100 participants are shown. The abbreviations employed to

Table 1.3. Summary of studies (n ≥ 100) reporting on the usefulness of the various ECG criteria for left ventricular hypertrophy detection in Caucasian and/ or African participants in mono- or multi-ethnic populations. The meaning of abbreviations is given at the end of the Table.

Reference; year; setting; location; (n)	Ethnicity	Study Participants; (% LVH)	% Female	Mean BMI[#] (kg/m^2)/ Wgt[§] (kg)	Sensitivity %	Specificity %	Accuracy %	AUC
Romhilt et al 1969; Hospital based; USA (n = 360)	Undefined	Deceased patients [Autopsied heart] (LVH = 44.4%)		-	SLV = 56.3 RaVL = 22.5 Lew = 17.5	SLV = 87.5 RaVL = 96.5 Lew = 98.5		
Devereux et al 1984 ; Hospital Based; USA (n = 148)	Multiethnic (61.5% Cau)	Hospital patients (LVH = 43%)	52.7		SLV = 23	SLV = 93	SLV = 62	
Casale et al 1987; Hospital Based; USA (n = 135)	Undefined	Deceased patients (LVH = 10%)	48.9		SLV = 22 CNV = 42	SLV = 100 CNV = 96	SLV = 60 CNV = 68	
McLenachan et al 1988 ; UK (n = 100)	Caucasian	Hypertensives (LVH = 39%)	35.0		SLV = 52 RaV = 32	SLV = 94 RaVL = 87		
Levy et al 1990b; Population Based (Framingham Heart Study); USA (n = 755)	Undefined (Caucasian)	Random population sample (LVH = 16.3%)	61.6		6.9 (for all ECG criteria used [incl SLV, RaVL] combined)	98.8 (for all ECG criteria used [incl SLV, RaVL] combined)		
Otterstad et al 1991; Norway (n = 100)	Caucasian	Moderate hypertensives (LVH = 48%)	0		SLV = 29 CNV = 2	SLV = 90 CNV = 100		
Lee et al 1992; Work Based; USA (n = 270)	Cau = 54.8% AA = 45.2%	Workers (members of labour unions) (LV H = 20% Cau, 26% AA)	30.7 (Cau = 24 AA=39)	Cau 28.0±4.7 # AA 27.7±5.0 #	**Cau AA** SLV = 15 17 CNV = 7 14 GUV = 7 3	**Cau AA** SLV = 95 73 CNV=100 93 GUV = 98 92		

Table 1.3. continued.

Reference; year; setting; location; (n)	Ethnicity	Study Participants; (% LVH)	% Female	Mean BMI[#] (kg/m^2)/ Wgt[§] (kg)	Sensitivity %	Specificity %	Accuracy %	AUC
Molloy et al 1992; Hospital Based; USA (n = 220)	Undefined	Deceased patients (LVH = 43.2%)	45.9		CNV= 36 CNPr= 51 SLV= 24 SLPr= 34 GUV= 19 GUPr= 15 12L = 31 RaVL= 13	95		
Fragola et al 1993 ; Italy (n = 200)	Caucasian	Mild to moderate essential hypertensives (LVH = 35%)	38.0		SLV = 29 GUV = 9 CNV = 23 Lew = 43 RaVL= 17	SLV = 89 GUV = 96 CNV = 96 Lew = 89 RaVL= 95		
Schillaci et al 1994; Italy (n = 923)	Caucasian	Hypertensives (LVH = 34%)	50.0		SLV = 21 GUV = 12 CNV = 16 RaVL= 14	SLV = 89 GUV = 97 CNV = 97 RaVL= 96		
Crow et al 1995 ; Hospital Based (Treatment of Hypertension Study); USA (n = 834)	Cau and AA	Mild hypertensives (LVH = 15%)	39.0		SLV = 8 CNV = 12 CNPr =11	SLV = 97 CNV = 96 CNPr = 97		
Okin et al 1995a; Hospital Based; USA (n = 389)	Undefined	Hospital patients (LVH = 29.8%)	29.0	-	CNV = 28 12L = 43 SLV = 43 GUV= 22 RaVL= 20 CNPr= 37 SLPr = 45 GUPr = 30	96		

Table 1.3. continued.

Reference; year; setting; location; (n)	Ethnicity	Study Participants; (% LVH)	% Female	Mean BMI[#] (kg/m^2)/ Wgt[§] (kg)	Sensitivity %	Specificity %	Accuracy %	AUC
Arnett et al 1997; Community Based; USA (n = 196)	African Americans	Random community sample (LVH = 32% men and 13% females)	-		Males CNV = 37.5 Females CNV = 0.7	Males CNV = 94.9 Females CNV = 94.6		
Okin et al 1998; Hospital Based; USA (n = 249)	Undefined	Hospital patients (LVH = 29.7%)	27.3	-	12L = 46 SLV = 43 SLPr= 54	98		
Chapman et al 1999; Hospital Based; UK (n = 408)	Cau = 66.4% AA = 33.6%	Hypertensives		-	Cau AA SLV = 22.5 44.9 CNV = 15.7 30.4	Cau AA SLV = 86.8 73.5 CNV =91.8 83.8		
Verdecchia et al 2000 ; Italy (n = 947)	Caucasian	Hypertensives (LVH = 27%)	41.0		SLV = 16 GUV = 13 CNV = 20	SLV = 93 GUV = 96 CNV = 91		
Jaggy et al 2000; Population Based ; Seychelles (n = 334)	African	Random population sample (LVH = 9.3%)	52.7	25.6 ± 4.6 #	SLV = 16 GUPr= 19 CNV = 19 CNPr= 26 CTV = 32	95		

Table 1.3. continued.

Reference; year; setting; location; (n)	Ethnicity	Study Participants; (% LVH)	% Female	Mean BMI[#] (kg/m^2)/ Wgt[§] (kg)	Sensitivity %	Specificity %	Accuracy %	AUC
					LVMI/$height^{2.7}$	LVMI/$height^{2.7}$	LVMI/ $height^{2.7}$	
					♂	♂	♂	
Malmqvist et al 2001; Research Clinic Based (Angina Prognosis Study In Stockholm [APSIS]); Sweden (n = 468)	Undefined (Caucasian)	Patients with stable angina pectoris (LVH = 19% [LVMI/$height^{2.7}$] and 15% [LVMI/BSA])	37.0	25.5±3.2 #	SLV = 92 GUV= 7 CNV= 4 CNPr= 9	SLV = 78 GUV= 100 CNV= 100 CNPr= 98	SLV = 7 GUV= 85 CNV= 84 CNPr= 84	
					♀	♀	♀	
					SLV = 97 GUV= 7 CNV= 15 CNPr= 17	SLV = 75 GUV= 100 CNV= 98 CNPr= 95	SLV = - GUV= 77 CNV= 78 CNPr= 77	
					LVMI/BSA	LVMI/BSA	LVMI/BSA	
					♂	♂	♂	
					SLV = 23 GUV= 8 CNV= 6 CNPr= 10	SLV = 90 GUV= 99 CNV= 99 CNPr= 98	SLV = 14 GUV= 92 CNV= 92 CNPr= 91	
					♀	♀	♀	
					SLV = 97 GUV= 14 CNV= 29 CNPr= 29	SLV = 87 GUV= 99 CNV= 97 CNPr= 96	SLV = 7 GUV= 89 CNV= 89 CNPr= 87	
Sundström et al 2001; Population based; Sweden (n = 475)	Caucasian	Random population sample (LVH = 28.2%)	0		SLV = 27 CNV = 17	SLV = 88 CNV = 91		

Table 1.3. continued.

Reference; year; setting; location; (n)	Ethnicity	Study Participants; (% LVH)	% Female	Mean BMI[#] (kg/m^2)/ Wgt[§] (kg)	Sensitivity %	Specificity %	Accuracy %	AUC
Gasperin et al 2002 ; Hospital Based ; Brazil (n = 306)	Multiethnic Cau = 87.3% Non - Caucasian = 12.7%	Outpatients scheduled for echocardiography (LVH = 27.8%)	57.5		Males SLV = 50.0 CNV = 38.2 Females SLV = 37.3 CNV = 54.9	Males SLV = 71.9 CNV = 90.6 Females SLV = 88.8 CNV = 81.6		
Okin et al 2002; Research Clinic Based (Losartan Intervention For Endpoint [LIFE] study); USA (n = 871)	Cau= 86.2% AA = 13.8%	Hypertensives (LVH = Cau 75.3% and Afr 70%)	Cau 43.0 Afr 30.8	Caucasians 27.0±4.1 # Africans 29.0±6.3 #	Cau AA SLV = 27 51 12L = 45 62 CNV = 57 49 SLPr= 47 69 CNPr= 76 67	Cau AA SLV = 69 44 12L = 59 44 CNV = 62 78 SLPr= 60 39 CNPr= 47 58		Cau AA SLV=0.50 0.49 12L =0.53 0.54 CNV=0.63 0.65 SLPr=0.53 0.52 CNPr=0.64 0.67
Martinez et al 2003 ; Spain (n = 250)	Caucasian	Mild hypertensives (LVH = 32%)	47.0		CNV = 19	CNV = 97		
Alfakih et al 2004; Hospital based ; UK (n = 288)	Undefined	Hypertensives (LVH = 38.6%)	41.7		SLV = 28.7 SLPr = 36.8 CNV = 21.3 CNPr = 31.1	SLV = 92.1 SLPr = 91.4 CNV = 94.8 CNPr = 91.4		
Salles et al 2005; Brazil (n = 471)	Cau, Afro Caribbean	Hypertensives with resistant hypertension (LVH = 81%)	72.0	28.8 #	SLV = 20 CNV = 24 CNPr = 32	SLV= 85 CNV= 89 CNPr= 85		
Dada et al 2005; Hospital Based; Nigeria (n = 100)	African	Hypertensives ≥ 18 years (LVH = 34%)	54.0	25.8 ± 5.0 #	SLV = 65.7 CNV= 25.7	SLV = 76.8 CNV= 88.8		SLV = 0.82 CNV = 0.76 SLR = 0.84 RaVL= 0.77

Table 1.3. continued.

Reference; year; setting; location; (n)	Ethnicity	Study Participants; (% LVH)	% Female	Mean BMI[#] (kg/m^2)/ Wgt[§] (kg)	Sensitivity %	Specificity %	Accuracy %	AUC
Sosnowski et al 2006; (n = 106)		CAD patients (LVH = 52%)	31.1	(LVH+) 28.2±4.3 # (LVH-) 27.7±3.8 #	CNV = 26.0 12L = 14.5 SLV = 13.0 SLPr = 27.0 CNPr= 25.5	95		CNV = 0.65 12L = 0.55 SLV = 0.54 SLPr = 0.64 CNPr= 0.70
Aktoz et al 2007; Hospital Based; Turkey (n = 125)	Undefined	Essential Hypertensives (LVH = 50.4%)	45.6	27.8#	SLV = 49 12L = 100 CNPr= 47 CNV ♂= 33 CNV ♀= 38	SLV = 98 12L = 27 CNPr= 100 CNV ♂= 97 CNV ♀= 100	SLV = 69 12L = 71 CNPr= 68 CNV ♂=59 CNV ♀=63	
Morrison et al 2007; Hospital Based; UK (n = 127)	Undefined	Hospital patients with cardiac abnormalities (LVH = 52.8%)	59.8	With LVH 28.0±5.9 # No LVH 27.3±6.5 #	SLV = 7.5 SLPr = 6.0 CNV = 7.5 CNPr = 14.9 GUV = 6.0 12L = 6.0 Lew = 11.9	SLV = 95.0 SLPr = 98.3 CNV =100.0 CNPr = 96.7 GUV = 95.0 12L = 91.7 Lew = 93.3		
Vottonen et al 2007; Population Based; Finland (n = 188)	Undefined (Caucasian)	Random middle aged population sample (LVH = 18.1%)	48.4		SLV = 29 SLPr = 47 CNV = 26 CNPr = 26	SLV = 88 SLPr = 85 CNV = 91 CNPr = 91		SLV = 0.73 SLPr = 0.70 CNV = 0.64 CNPr = 0.63
Martin et al 2007; Hospital Based; Antigua (n = 111)	Afro-Caribbean	Hypertensives (LVH = 49.5%)	66.7		SLV = 31 CNV = 23 12L = 25	SLV = 86 CNV = 96 12L = 80		
Mazzaro et al 2008; Hospital Based; Brazil (n = 1204)	Undefined	Systemic arterial hypertension (SAH) patients	48.8		SLV = 13.4 CNV = 18.8 CNPr = 22.2	SLV = 96.8 CNV = 96.8 CNPr = 96.0	SLV= 66.3 CNV= 68.3 CNPr=69.0	

Table 1.3. continued.

Reference; year; setting; location; (n)	Ethnicity	Study Participants; (% LVH)	% Female	Mean BMI[#] (kg/m^2)/ Wgt[§] (kg)	Sensitivity %	Specificity %	Accuracy %	AUC
Casiglia et al 2008; Population Based (Cardiovascular Study in the Elderly [CASTEL] and of the Last Evidences Of Genetic Risk factors in the Aged [LEOGRA]); Italy (n= 1699)	Undefined	Random population sample (LVH = 36.6% in males and 53.4% in females)	58.4	26.6±4.3 #	≤ 69 years ♂ ♀ SLV=17.0 10.3 CNV= 5.9 10.3 Lew=16.0 13.1 RaV = 8.0 5.2 > 69 years ♂ ♀ SLV=16.7 12.7 CNV= 3.8 10.1 Lew=10.9 16.7 RaV = 7.1 7.9	≤ 69 years ♂ ♀ SLV=90.8 82.5 CNV=99.3 96.1 Lew=92.1 86.4 RaVL=94.2 92.2 > 69 years ♂ ♀ SLV=97.6 93.7 CNV=97.6 97.2 Lew=93.7 89.7 RaVL=63.4 93.1		
Ang et al 2008; Hospital Based; UK (n = 241)	Caucasian	CAD patients (LVH = 73% [LVMI/height$^{2.7}$] and 46% [LVMI/BSA])	24.0	29.0±4.0 #	SLV = 8.4 CNV = 6.8 GUV = 5.1 Lew =11.4 RaVL = 6.8 CNPr =10.2 12L = 2.8	SLV = 90.0 CNV = 87.6 GUV = 95.4 Lew = 86.2 RaVL = 93.8 CNPr = 96.9 12L = 100		SLV = 0.50 CNV = 0.47 GUV = 0.50 Lew = 0.49 RaVL = 0.50 CNPr = 0.54 12L = 0.51
da Costa et al 2008; Hospital Based; Brazil (n = 1204)	Undefined	Hypertensive patients	70.8		BMI <30 ≥30 CNV =18.8 18.9 CNPr=22.4 21.9 SLV =17.5 3.7 RaVL=10.3 11.3	BMI <30 ≥30 CNV =96.5 97.6 CNPr=95.4 97.6 SLV =96.5 97.6 RaVL=96.3 97.2		
Rogers et al 2008; Hospital Based; USA (n = 352)	Undefined	Hospital patients with heart abnormalities – suspected heart failure (LVH = 54.8%)	34.4		CNV = 34 CNPr = 60	CNV = 91 CNPr = 73		

Table 1.3. continued.

Reference; year; setting; location; (n)	Ethnicity	Study Participants; (% LVH)	% Female	Mean BMI[#] (kg/m^2)/ Wgt[§] (kg)	Sensitivity %	Specificity %	Accuracy %	AUC
Vanezis and Bhopal 2008; Meta-analysis; USA and UK (n = 5619)	Bi-ethnic: Cau = 87.4%, Afr = 12.6%	Random population samples and selected participants	50.0		**Cau Afr** SLV = 18.2 32.9 CNV= 26.5 31.2	**Cau Afr** SLV = 88.9 72.1 CNV= 87.4 86.2		
Rodrigues et al 2008; Population Based (MONICA-Vitória Project); Brazil (n = 682)	Multiethnic : Cau = 18.8% Mul = 25.7% Afr = 2.8% Other= 52.7%	Random population sample (LVH = 23.7%)	56.5	Males 26.1±3.6 # Females 26.8±5.2 #	Males CNV = 22.5 Females CNV = 28.0	95		
Buchner et al 2009; Hospital Based; Germany (n = 120)	Undefined	Patients with aortic valve disease (LVH = 86%)	35.0		GUV = 34 SLV = 57 SLPr = 51 CNV = 52 CNPr = 56 LVMI >93g/m^2	GUV = 90 SLV = 90 SLPr = 96 CNV = 87 CNPr = 87 LVMI>93g/m^2	GUV = 52 SLV = 67 SLPr = 65 CNV = 63 CNPr = 66	GUV = 0.72 SLV = 0.80 SLPr = 0.86 CNV = 0.78 CNPr= 0.81 LVMI>93g/m^2
Sohaib et al 2009; Workplace Based (LARGE Heart Study; UK (n = 101)	Caucasian	Male army recruits	0	73.6 ± 9.8 §	SLV = 38.7 SLPr = 43.4 CNV = 19.4 CNPr = 22.6	SLV = 74.3 SLPr = 61.4 CNV = 91.4 CNPr = 85.7		SLV = 0.61 SLPr = 0.62 CNV = 0.52 CNPr = 0.53
Truong et al 2010; Hospital Based (Rule Out Myocardial Infarction Using Computer Assisted Tomography [ROMICAT] trial); USA (n = 333)	Multiethnic; Afr = 9% Other = 91%	Patients presenting at the hospital with acute chest pain (LVH = 7.2% [LVMI/$height^{2.7}$] and 6.9% [LVMI/BSA])	37.0	29.0 #	[LVMI/$height^{2.7}$] CNV = 17 [LVMI/BSA] CNV = 22	[LVMI/$height^{2.7}$] CNV = 96 [LVMI/BSA] CNV = 97		

Table 1.3. continued.

Reference; year; setting; location; (n)	Ethnicity	Study Participants; (% LVH)	% Female	Mean BMI[#] (kg/m^2)/ Wgt[§] (kg)	Sensitivity %		Specificity %		Accuracy %	AUC
				LBBB +	LBBB +	-	LBBB +	-		
Rodr□guez-Padial 2012 ; Hospital Based; Spain (n = 1875; LBBB+ = 233, LBBB- =1561)	Undefined	Hospital patients with heart abnormalities (LVH = 60.5% [LBBB+] and 37.8% [LBBB-])	46.8	31.3±27.6 #	CNV =19.1	6.5	CNV =95.7	99.3		CNV = 0.70
					12L = 10.6	6.5	12L = 96.7	96.0		12L = 0.66
				LBBB -	SLV =10.6	3.5	SLV =97.8	96.2		SLV = 0.52
				30.3±27.2 #	GUV= 6.4	5.2	GUV=100	98.6		GUV= 0.59
					RaVL= 8.5	10.0	RaVL=97.8	96.6		RaVL= 0.63
					Lew =15.6	19.0	Lew =95.7	93.4		Lew = 0.58
					CNPr= 34.0	12.3	CNPr=92.4	97.4		CNPr= 0.72
					SLPr = 16.3	5.2	SLPr =93.5	96.9		SLPr = 0.57
					GUPr =17.7	13.3	GUPr=94.6	95.6		GUPr= 0.62
Gosse et al 2012; Research Clinic Based (The Bordeaux Cohort); France (n = 958)	Undefined	Untreated Hypertensives (LVH = 41%)	39.4	74.0±15.0 §	SLV = 10		SLV = 92			SLV = 0.52
					SLPr = -		SLPr = -			SLPr = 0.54
					CNV = 12		CNV = 93			CNV = 0.67
					CNPr = 13		CNPr = 93			CNPr = 0.67
					RaVL = 18		RaVL = 94			RaVL = 0.72

CNV- Cornell voltage; CNPr – Cornell product; SLV – Sokolow-Lyon Voltage; SLPr – Sokolow-Lyon product; GUV – Gubner-Ungerleider voltage, GUPr - Gubner-Ungerleider product; 12L – 12 Lead QRS sum; RaVL – R wave in lead aVL; CTV – Composite time voltage; # - Mean BMI, § - Mean body weight; Lew – Lewis voltage; Mul – Mulatto; LBBB - Left branch bundle block; LBBB+ - Patients with left branch bundle block; LBBB- - Patients without left branch bundle block; LVMI – Left ventricular mass index; BSA – Body surface area; Cau – Caucasian; Afr – African; CAD – Coronary artery disease; NCEP – National Cholesterol Education Program.

define each criterion are provided in both Table 1.2 and at the end of Table 1.3. The most commonly used and the best validated ECG criteria, the Sokolow-Lyon and Cornell voltage criteria, as well as alternative ECG criteria generally have high specificities but low sensitivities and their performance for LVH detection is poor (see Table 1.3). The product of QRS voltages and the QRS duration can improve the identification of LVH by ECG criteria, as evidenced by higher sensitivities at comparable specificities in some studies and an improved overall performance (Table 1.3). Although multiplying the voltages by the QRS duration may improve LVH detection, the improvement is only small in some instances with the Cornell product performing only slightly better than the Cornell voltage criteria (Table 1.3). Moreover some studies have failed to show improvement in performance when assessing the duration product (Table 1.3). The very poor sensitivity and high specificity of all ECG criteria make them poor diagnostic tests for excluding the presence of LVH.

Importantly, most of the studies assessing the performance of ECG criteria for LVH detection were carried out in Caucasian and not in mixed populations. Very few studies have been conducted in Africans in Africa. The studies that were performed in Africa have small sample sizes (Dada et al [2005] conducted in Nigeria (n=160) and Jaggy et al [2000] conducted in the Sychelles (n=334)) and these studies have conflicting results (Jaggy et al 2000, Dada et al 2005). Whilst Jaggy et al (2000) noted that the use of all the standard ECG criteria were invalid in the Sychelles population and proposed a new Composite Time Voltage criteria (Jaggy et al 2000), Dada et al (2005) confirmed the superiority of the Sokolow-Lyon voltage criterion over the other criteria. Albeit that ECG criteria for LVH detection have a low sensitivity and a generally poor performance for LVH detection, an important question is how well do these criteria predict cardiovascular risk?

1.2.2 Evidence for the prognostic value of ECG criteria for LVH detection

In a recent review, the importance of ECG criteria for LVH detection for risk stratification in hypertension was underscored and the use of Cornell voltages was recommended for this purpose (Schillaci et al 2012). In this regard, changes in ECG criteria for LVH with antihypertensive therapy have prognostic relevance. Table 1.4 summarises some of the longitudinal/intervention studies that show the prognostic value of various ECG criteria. Some of the studies are worthy of specific mention.

Importantly, ECG voltage criteria have been found to predict cardiovascular outcomes independent of echocardiographic LVM (Sundström et al 2001, Schneider et al 2004). In the Framingham Heart Study, a decline in Cornell voltages was associated with a decrease in the risk, whilst increases in Cornell voltages were associated with an increased risk of CVD (Levy et al 1994). The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated an improved prognosis with regression of ECG LVH in response to ramipril-based therapy (Mathew et al 2001). Moreover, in the Multiple Risk Factor Intervention Trial (MRFIT) conducted in a very large study sample (n = 12866) a continuous change in ECG LVH was noted to be a strong independent predictor of CVD and coronary heart disease mortality (Prineas et al 2001). Furthermore, in a large study performed in hypertensive patients with ECG evidence of LVH (n = 9193), the aforementioned LIFE study, the regression of ECG-LVH from baseline values after just 6 months was associated with composite cardiovascular events, mortality, stroke and myocardial infarction, suggesting that ECG detection of LVH is important in the monitoring of treatment outcomes (Okin et al 2004a, Okin et al 2004b). In this regard, the LIFE study provided significant evidence to support the use of both Sokolow-Lyon and Cornell product criteria in the identification of LVH and the monitoring of hypertensive patients on antihypertensive therapy (Okin et al 2004a, Okin et al 2004b).

Table 1.4. Summary of large or relatively large studies reporting on the prognostic relevance of electrocardiographic (ECG) criteria for left ventricular hypertrophy. The meaning of abbreviations is given at the end of the Table.

Reference; year; study; location	Ethnicity	Criteria	Mean BMI	n	% Female	Study design	Findings
Levy et al 1994; Framingham Heart Study; USA	Undefined	SLV, CNV, RaVL	-	524	47.7	Longitudinal study	Regression of ECG LVH was associated with a reduction in the risk of cardiovascular disease.
Vedercchia et al 1998; Progeto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study; Italy	Caucasian	Perugia score, CNV, SLV, Rhomhilt Estes, Framingham, left ventricular strain	26.5 ± 4.0	430	46	Prospective	ECG LVH identifies individuals at cardiovascular risk
De Bacquer et al 1998; Belgian Inter-University Research on Nutrition and Health (BIRNH) study; Belgium	Caucasian	ST-T strain, LAD, Minnesota code	Males 25.9 ± 3.5 Females 25.9 ± 4.5	9954	47.7	Prospective cohort	Baseline ECG abnormalities are strongly associated with subsequent all cause, CVD, and CHD mortality with similar predictive value for men and women.
Mathew et al 2001; Heart Outcomes Prevention Evaluation (HOPE) study; USA	Multiethnic (90.1% Caucasian)	SLV, ST-T strain, LAD	28 ± 4	8281	26.3	double-blind, placebo-controlled, intervention study	Ramipril treatment (an ACE inhibitor) causes ECG-LVH regression independent of ↓ BP and a ↓risk of stroke, MI, CHF and death.
Okin et al 2004a; Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study; USA	Undefined	SLV, CNPr	-	9193	54	Randomised, double blind prospective study	Both ↓ ECG LVH detected by the SLV and CNPr due to LVH regressing and preventative antihypertensive therapy was associated with ↓ likelihoods of CV morbidity and mortality independent of blood pressure lowering.

Table 1.4. continued.

Reference; year; study; location	Ethnicity	Criteria	Mean BMI	n	% Female	Study design	Findings
Okin et al 2004b; Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study; USA	Multiethnic : ~14.4% Afr	SLV, CNV	27.3 ± 4.4	584	40.2	Double-blind, prospective, intervention study	↓ LVM is associated with ECG LVH (CNPr) regression and a > anatomic LVH regression likelihood.
Hsieh et al 2005; USA	Multiethnic : 72.9% Cau 16.8% Afr 10.3% Other	SLV, CNV, CNPr, 12 Lead QRS sum, Minnesota code 3.1, Framingham score, Perugia score, Romhilt-Estes score	26.5 ± 3.5[§] 30.2 ± 6.7[#]	19434	0	Prospective study	ECG LVH showed very good prognostic significance although there was no outstanding criterion.
Antikainen et al 2006; Department of Health and Social Security Hypertension Care Computer Project (DHCCP); UK	Undefined	SLV		6668	50.1	multicentre computer-based observational study	High ECG voltages at baseline are associated with a high CVD mortality risk. For each quantitative 0.1 mV increase in baseline ECG voltage there was a significant ↑ in the risk of stroke, CHD and CVD. Even after adjustments for race, BMI, smoking and SBP, women with LVH tended to have a higher risk of stroke mortality.
Verdecchia et al 2007; The Hypertrophy at ECG And its Regression during Treatment (HEART) Study; Italy.	Undefined	CNV, Perugia score, ST strain, Romhilt- Estes score	28.1 ± 4.0	496	50.2	Prospective study	ECG LVH and its serial changes has great prognostic value and identifies individuals at an increased cardiovascular risk.

Table 1.4. continued.

Reference; year; study; location	Ethnicity	Criteria	Mean BMI	n	% Female	Study design	Findings
Antikainen et al 2009; Department of Health and Social Security Hypertension Care Computer Project (DHCCP); UK	Undefined	SLV		5395	49.4	multicentre computer-based observational study	Despite the low sensitivity, ECG LVH in overweight subjects is a good predictor of mortality

Cau – Caucasian; Afr – African; Hisp – Hispanic; SLV – Sokolow Lyon Voltage; CNV – Cornell Voltage; CNPr – Cornell Product; CVD – Cardiovascular disease; CHD – Coronary heart disease; ↑ - increased; ↓ - decreased; # - participants with LVH ; § - participants without LVH; LAD – Left axis deviation; SBP – Systolic blood pressure.

The aforementioned studies summarised in Table 1.4, highlight the importance of providing evidence for the usefulness of the various ECG criteria in the African context. Evidence to show support for the use of ECG criteria for LVH detection would be of economic value to a country such as South Africa, where echocardiographic (or other more sophisticated measures) approaches to LVH detection are not recommended for routine use because of the cost and resource implications. Despite the arguments in favour of using ECG criteria for LVH detection in routine risk prediction, there is evidence to indicate that a number of factors may influence the performance of these criteria. In the subsequent discussion I will highlight the evidence to suggest that correlations with determinants of LVH or with echocardiographic assessments of LVM, and the sensitivity, specificity and performance of ECG criteria for LVH detection may differ in groups of African ancestry and in the obese, highlighting the evidence that prompted me to perform the studies described in the present thesis.

1.2.3 Impact of ethnicity on the electrocardiographic detection of left ventricular hypertrophy.

One of the major factors that may influence the performance of ECG criteria for LVH detection and potentially affect their universal usefulness is ethnicity. Ethnic variations in ECG recordings have been noted in many studies with several ECG variables. In this regard, Table 1.5 provides a summary of studies that show the influence of ethnicity on ECG detected LVH prevalence and variations in ECG parameters employed in calculating ECG LVH. In this regard, there are a number of reports to suggest that QRS complex voltages (particularly R_{V5}, R_{aVL} and S_{V1}) are higher in Africans than in Caucasians (Munro-Faure et al 1979, Rautaharju et al 1994, Chaturvedi et al 1994, Vitellli et al 1998, Chapman et al 1999, Spencer et al 2004, Jain et al 2010). Initially, these higher voltages were thought to represent a higher prevalence of LVH. However, subsequently, it was hypothesised that these effects may be attributed to a

Table 1.5. Summary of studies reporting on the effects of ethnicity on electrocardiographic (ECG) parameters used in determining left ventricular hypertrophy. The meaning of abbreviations is given at the end of the Table.

Reference, location, Participant group	Study and period	Ethnicity	n	% Female	Findings
Munro - Faure et al 1979; United Kingdom; Hospital-based; Hypertensives from hospital records.		Biracial: 87.2% Cau, 12.8% Afr	1110		African patients had a higher prevalence of ECG LVH (40%) than Cau (18%) [Mean S_{V1} + R_{V5} or 6 = 32.6 ± 10.32 mm (Afr) and 25.9 ± 8.48 mm (Cau)]
Lee et al 1992, USA; Worksite-based; Hypertensive workers,	1981 – 1983	54.8% Cau, 45.2% AA	240	30.8	Echo LVH was 20% in Ca and 26% in AA (ns). ECG LVH = 6% - 24% (AA), 1% - 7% (Ca). (2.4x - 6x higher in AA than Cau). Sensitivity was low in both races, but specificity was consistently lower and significant in AA. Both positive and negative predictive values were lower in AA. BMI was inversely related to the likelihood of a false positive ECG. Hence ECG criteria are poor tools for LVH detection in AA.
Sutherland et al 1993; Minnesota, USA; Population based; Randomly selected.	Charleston Heart Study (CHS); 1960 – 1987	Biracial: 58.8% Cau, 41.2% AA	993	0	AA had a higher occurrence of T wave inversions. Major ECG abnormalities predicted that Caucasians were more likely to die from CHD (2.72x) than Africans (1.95x).
Rautaharju et al 1994; USA; Population-based; randomly selected.	NHANES II; 1976-1980, Hispanic Health and Nutrition Examination Survey; (HHANES II) 1982-1984	57.0% Cau, 7.3% AA, 35.7% Hisp	13842	54.5	The R wave amplitudes of leads V5 and aVL and the S wave amplitudes of V1 and V3 were higher in both male and female AA than in Cau and Hisp. There was a consistent ↓ in R_{V5}, but an ↑ in R_{aVL} with an increase in BMI. There was a left axis shift in obesity more pronounced in AA than Cau. CNV ↑ with age whilst SLV ↓ with age.
Chaturvedi et al 1994 United Kingdom; Population-based; Randomly selected.		Biracial: 50.1% Cau, 49.9% Afr	1160	55.6	Normotensive Afr participants had a significantly higher prevalence of tall R waves than Cau. Wall thickness was greater in hypertensives than normotensives and greater in Afr than in Cau. In both Afr and Cau, IVST and LVMI was significantly higher in individuals with tall ECG R waves whilst LVEDD was significantly lower even after adjusting for body size.

Table 1.5. continued.

Reference, location, Participant group	Study and period	Ethnicity	n	% Female	Findings
Arnett et al 1997 Minnesota, USA ; Population-based; Randomly selected.	Charleston Heart Study (CHS); 1987	African American	196		The diagnostic accuracy of the Cornell ECG criteria in AA was comparable to that previously reported in Cau. The Cornell criteria had the highest sensitivity in women.
Vitelli et al 1998 USA; Population-based ; Randomly selected.	The Atherosclerosis Risk in Communities Study (ARIC)	81.6% Cau, 18.4% AA	2686	69.7	QRS intervals were shorter in AA men than in Cau men.The corrected QT (QTc was longer in women than in men and longer in Cau than in AA. AA had significantly higher Cornell voltages. QRS voltages were higher in AA than Cau.
Chapman et al 1999 England; Research Clinic-based; Hypertensives.		Biracial: 66.4% Cau, 33.6% Afr	408		ECG voltages were > in Afr than Cau with a higher ECG LVH sensitivity (2x), but the overall performance after adjustments made ECG detection of LVH very poor. Chapman proposed that current ECG criteria for LVH have a greater or equal value in Afr as compared to Cau.
Rautaharju et al 2000 USA ; Multicentre, Population-based ; Randomly selected >65 years.	Cardiovascular Health Study; 1989 – 1995	86.1% Cau, 13.9% AA	3627	63.3	Echocardiographic LVH (unadjusted for body size differences) was not significantly different between AA and Cau. Both SLV and Cornell voltage were significantly higher in AA men and women whilst T wave amplitudes in V5 and V6 were significantly lower in AA than in Cau. Therefore higher QRS amplitudes do not necessarily reflect increased echo LVM in AA
Jaggy et al 2000 Seychelles ; Population-based ; Randomly selected between 25-64 years of age.		African	334	52.7	The standard ECG criteria had poor sensitivities at the normal cut off values. The best accuracy was obtained with the RaVL voltage criterion. All ECG criteria had lower sensitivities than those obtained in Cau populations. The new Composite Time Voltage criterion outperformed all the others.

Table 1.5 continued.

Reference, location, Participant group	Study and period	Ethnicity	n	% Female	Findings
Okin et al 2002 USA; Research clinic-based; Hypertensives.	Losartan Intervention For Endpoint (LIFE) Study	Biracial: 86.2% Cau, 13.8% AA	871		SLV and 12L voltages were significantly higher in AA than in Cau, but CNV voltage was lower in AA. SLV and 12L specificities were lower in AA whilst the specificity of CNV was higher. SLV and 12L underestimated whilst CNV overestimated LVH in AA.
Spencer et al 2004 Research hospital-based; Hypertensives.		Multiethnic: 64% Cau, Afro-Caribbean = 11%, South Asian = 25%	380	19.7	ECG voltages in Cau and South Asians were similar, but lower than in Afro-Caribbean hypertensives. ECG LVH prevalences were significantly different for the SLV and RaVL criteria amongst the all races.
Dada et al 2005 Nigeria; Research Clinic; Hypertensives and controls		African	160		Hypertensive participants had the highest LVH prevalence. Many criteria had too many false positives and false negatives. The SLV outperformed all the other ECG criteria.
Martin et al 2007 West Indies; Hospital-based; Hypertensives.		African	111	67	All the ECG criteria had low sensitivities and specificities. Although the SLV was the best criteria, overall, all the ECG criteria were not useful in the Afro Caribbean population because they were not sensitive enough to detect ↑ echo LVH.
Vanezis and Bhopal 2008; Meta-analysis; USA and UK		Bi-ethnic: Cau = 87.4%, Afr = 12.6%	5619	50.0	Sensitivity was generally low in both Afr and Cau groups, but Afr groups had slightly higher sensitivities than Cau groups. Specificity was high in Cau for both CNV and SLV, but low in Afr groups for the SLV only.
Jain et al 2010 USA;Population-based; Random sample	Multi-Ethnic Study of Atherosclerosis (MESA)	Multiethnic: Caucasian = 38.8%, African American = 25.7%, Hispanic = 22.3%, Chinese = 13.2%	4967	52.4	Sensitivities were highest in AA, at the lowest specificities. Cau had the lowest RV5 amplitudes. Sensitivities were low at high specificities. Although the SLV was the most sensitive the performance was still very poor.

Cau – Caucasian; AA – African American; Afr – African; Hisp – Hispanic; NHANES – National Health And Nutrition Examinations Survey; IVST – Interventricular septal wall thickness; CHD – Coronary heart disease; SLV – Sokolow – Lyon Voltage; CNV – Cornell Voltage; ↑ - increased; ↓ - decreased; LVM – Left ventricular mass; LVMI – Left ventricular mass index; LVEDD – Left ventricular end diastolic diameter; MAP – mean arterial pressure; PP – Pulse pressure; RWT - Relative wall thickness.

decrease in skin conductivity (Krovetz 1994) or a diminished thoracic diameter reducing the distance from the skin surface to the heart (Walker et al 1972, Ashcroft 1972, Horton et al 1977). These hypotheses were introduced to explain the fact that the increased QRS complex amplitudes may translate into a significantly higher prevalence of ECG-detected LVH than echocardiographically-detected LVH (Lee et al 1992, Rautaharju et al 2000); higher values for Sokolow-Lyon and 12-lead criteria for LVH (Okin et al 2002, Rautaharju et al 2000); a poor specificity for Sokolow-Lyon and 12-lead criteria for LVH detection when compared to echocardiograph-detected LVH (Okin et al 2002, Dada et al 2005, Martin et al 2007, Jain et al 2010); and also possibly a poor sensitivity for LVH detection (Jaggy et al 2000, Martin et al 2007) in groups of African descent as compared to Caucasians. In this regard however, ECG criteria for LVH detection have nevertheless also been shown to be more sensitive in groups of African descent (Chapman et al 1999, Jain et al 2010).

There are other differences in ECG recordings in groups of African ancestry. In this regard, T-wave inversions may also occur more frequently in Africans than in Caucasians (Keys 1970, Sutherland et al 1993, Rautaharju et al 1994, Ashley et al 2000, Vanezis and Bhopal 2008), and T waves have been shown to have lower voltages in African-Americans as opposed to Caucasians (Rautaharju et al 2000), a change that may reflect an intermediate phase of T-wave inversion. African-Americans also exhibit shorter QT intervals corrected for heart rate (Vitelli et al 1998, Vanezis and Bhopal 2008), a change which may reflect an earlier onset of repolarisation.

1.2.2 Impact of obesity on the electrocardiographic detection of left ventricular hypertrophy.

In addition to a number of alternative changes in the heart in both structure and function, alterations which go beyond the scope of the present thesis, obesity is associated with marked increases in LVM and the prevalence of LVH, with a strong

residual relationship existing between obesity and LVM even after adjustments for age and BP (Lauer et al 1991, Schmeider and Messerli 1993, de Simone et al 1994, Gottdiener et al 1994, de Simone et al 1996, Hanevold et al 2004, Chinali et al 2006). The question which arises is therefore whether ECG measurements in the obese are able to accurately detect alterations in the heart associated with obesity?

Morbid obesity prolongs the duration of the P wave. Indeed, 17% of morbidly obese normotensive participants (n = 100) as compared to 0% of normal weight normotensive participants (n = 100) have a P wave duration > 120ms in lead II (Alpert et al 2000). The prolonged P wave duration may reflect an enlarged right atrium. Obesity is also associated with a left axis shift that is directly proportional to the severity of obesity (Frank et al 1986) and is more pronounced in Africans than Caucasians (Rautaharju et al 1994). A substantial weight loss has been associated with a significant rightward return of the axis in the morbidly obese (Alpert et al 2001). In uncomplicated obesity, left axis deviations are however, not as common as in morbid obesity (Fraley et al 2005). Obesity is also associated with flattening of T-waves in leads II, III, aVF, V5 and or V6, and inversion/flattening of the T-wave in leads aVL and I (Alpert et al 2000). This occurs in almost 50% of all morbidly obese participants (Alpert et al 2000) and this effect is reversed after significant weight loss (Alpert et al 2001). The obesity-induced T wave flattening is probably due to a horizontal and leftward displacement of the base of the heart produced by abdominal adiposity (Fraley et al 2005).

With respect to the impact of obesity on ECG criteria for LVH detection, the presence of obesity may markedly attenuate QRS amplitudes (Frank et al 1986, Alpert et al 2000), particularly over chest leads, and hence diminish the capacity to detect LVH using ECG criteria. This has been postulated to be the result of an increased distance between the precordial leads and the heart due to accumulation of adipose tissue (Nath et al 1988). Importantly, weight reduction is associated with an increase in QRS voltages (Alpert et al 2001). Table 1.6 summarises studies showing the effects of obesity on ECG parameters used to detect LVH. As a consequence of the reduced QRS amplitudes,

Table 1.6. Summary of studies reporting on the effects of obesity on electrocardiographic (ECG) parameters used in calculating left ventricular mass.

Reference, location, Setting	Study and period	Ethnicity	n	% Female	Group	Findings
Frank et al 1986; Washington DC, USA; Research Clinic.		Undefined	1029	85	Obese patients	Obesity is positively correlated to heart rate and QRS duration and a left axis shift, but negatively correlated to QRS voltage.
Nath et al 1988; Missouri, USA; Multicenter, Research Clinic.		Multiethnic: 93.8% Cau, 6.2% AA	65	87.7	Obese patients	RaVL had the highest sensitivity. Generally low sensitivity was associated with high specificity. ECG criteria underestimate LVH in extreme obesity.
McLenachan et al 1988; Hospital based; UK		Caucasian	100	35	Hypertensives	ECG criteria based on limb leads were more sensitive for detection of LVH in obese hypertensives whilst the CG criteria based on chest leads was more sensitive in non-obese hypertensives
Abergel et al 1996; Paris, France; Hospital based.	Jan - Sept 1993	Undefined	349	41.5	Hypertensive patients	CNV was better correlated to LVM than SLV which performed poorly in the obese, but CNV performance was similar in the obese and non obese.
Okin et al 1996b USA; Hospital; Multicenter, Research.			212	46.7	Deceased patients	The Cornell voltage criteria showed the best performance in obese individuals.
Alpert et al 2000 USA; Research Clinic.		Undefined	200	85	Morbidly obese patients	Obesity was associated with ↓ QRS voltage, flattening of T - wave in leads II, III, aVF, V5 and or V6, and inversion/flattening of T-wave in leads aVL and I.
Okin et al 2000 USA; Research Clinic.	LIFE Study, 1996	Multiethnic: > 88% Cau, > 4.5% AA, > 1.3% Other	8417	> 55	Hypertensive patients	There is a strong link between obesity and ECG LVH. CNV was positively correlated whilst SLV was negatively correlated to obesity.
da Costa et al 2008 Sao Paulo; Brazil; Research clinic.		Multiethnic: (Mainly Cau with a few Afr and a few Brazilian mulattoes)	1204	70.8	Hypertensive patients	Obesity did not ↓ specificity in all ECG criteria and sensitivity in the Cornell and RaVL criteria, but ↓ sensitivity in Sokolow - Lyon criteria. (29.3% of participants were obese)
Smith et al 2010 Research Clinic; Utah, USA.		Undefined	747	82	Severely obese patients	Obesity dampened the LVH detection ability of all ECG criteria although the RaVL criteria was the most sensitive of all.
Domienik-Karlowicz et al 2011; Research Clinic; Warsaw, Poland.		Udefined (Caucasian)	95	84.2	Morbidly obese patients	None of the ECG criteria were of value in the diagnosis of LVH although the Cornell Product showed performance that was better than the other criteria.

Cau – Caucasian; AA – African American; Afr – African; Hisp – Hispanic; SLV – Sokolow – Lyon Voltage; CNV – Cornell Voltage; ↑ - increased; ↓ - decreased; RaVL criterion – ECG R wave in aVL criterion.

particularly over chest lead recordings (Frank et al 1986, Alpert et al 2000), criteria which rely heavily on chest lead recordings such as the Sokolow-Lyon criteria show a negative correlation with indices of adiposity (Okin et al 2000) and a markedly reduced performance and sensitivity for LVH detection (Abergal et al 1996, Okin et al 1996b, da Costa et al 2008). In contrast, criteria which depend more on limb lead QRS amplitudes, such as RaVL and Cornell voltage criteria are positively correlated with obesity (Okin et al 2000), and have a higher performance and sensitivity for LVH detection in obesity (Nath et al 1988, Abergel et al 1996, Okin et al 1996b, da Costa et al 2008, Smith et al 2010, Dominiek-Karlowicz et al 2011). Importantly, obesity does not appear to significantly diminish the specificities of ECG criteria for LVH detection, and obesity may not affect the sensitivity of RaVL, Cornell voltage and Cornell product criteria for LVH detection (da Costa et al 2008). However, in the morbidly obese (body mass index [BMI] ≥ 40 kg/m^2; n = 85), the very low sensitivity of 2% at 98% specificity of the Cornell product, suggests that even those criteria which rely more on limb-lead recordings for LVH detection are of little value in these individuals (Domienik - Karlowicz et al 2011).

1.2.3 Impact of coexistent obesity on the electrocardiographic detection of left ventricular hypertrophy in groups of African descent.

As highlighted in the previous sections, both African ancestry and obesity may affect the ability of ECG criteria to detect LVH. The question which arises from this evidence is whether the combined effects of obesity and African ethnicity may render ECG criteria for LVH detection invalid? In this regard, although one study has demonstrated that the left axis shift which occurs in obesity is more pronounced in Africans than in Caucasians (Rautaharju et al 1994), there are no studies that have examined the impact of obesity on ECG criteria for LVH detection specifically in groups of African descent. Therefore, in the present thesis I explored the question of the impact of obesity on ECG criteria for LVH detection in a group of African descent with a high

prevalence of obesity. These data and the implications thereof are discussed in chapters 2 and 3 of the present thesis. These data have been published in the *Journal of Hypertension* (Maunganidze et al 2013a).

1.3 Prevalence of left ventricular hypertrophy in groups of African ancestry: A need for identifying possible mediators of this effect.

The higher prevalence of LVH in Africans as compared to Caucasians has been established in a number of studies (Koren et al 1993, de Simone et al 1994, Gardin et al 1995, Zabalgoitia et al 1998, Skelton et al 2003, Kizer et al 2004, Rodriguez et al 2004, Drazner et al 2005). Importantly, these differences have been noted in large, randomly selected, population-based studies. Indeed, in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a prospective multicentre study in the United States of America (n = 4243, age range = 23 to 35 years), echocardiographically-determined LVM was higher in African (167 ± 43 g) than in Caucasian (156 ± 50 g, $p < 0.0001$) men as well as in African (142 ± 49 g) as compared to Caucasian (137 ± 43 g, $p < 0.002$) women after adjustments for confounding variables (Gardin et al 1995). The Northern Manhattan Study (NOMAS), a multiethnic population-based cohort study, also demonstrated higher mean echocardiographically-determined LVMI values for Africans (48.9 $g/m^{2.7}$) than Caucasians (45.6 $g/m^{2.7}$, $p= 0.0004$) (Rodriguez et al 2004). In addition, in the Hypertension Genetic Epidemiology Network (HYPERGEN) Study, greater echocardiographically-derived LVM values were noted in Africans (173.1 ± 40.9 g, n=1060) in comparison to those identified in Caucasians (167.1 ± 39.4 g, n = 580, p=0.009), even after adjustment for confounding variables (Kizer et al 2004). More importantly, using magnetic resonance imaging, which is a more accurate method of assessing LVM than echocardiography, in the Dallas Heart Study consisting of non-institutionalised randomly selected individuals (n=2193), 60.9% of which were Africans, the prevalence of LVH was noted to be 2-3 times higher in Africans (47% in women and 25% in men) than in Caucasians (22% in women and 8.7% in men,

p= 0.001) (Drazner et al 2005). In addition, in that study LVM was noted to be on average markedly higher in African-American as compared to European-Americans even after adjustments for confounders including socioeconomic status, fat free mass, gender, age and systolic BP (Drazner et al 2005).

The high prevalence of LVH in groups of black African ancestry suggests that this group may be at a high risk for cardiovascular events and that there is therefore a distinct need for identifying LVH in this ethnic group. However, as indicated in previous sections of this chapter, the ability to identify ECG LVH in this ethnic group may be considerably diminished and this effect may be further exacerbated by obesity. It is therefore important that alternative methods for LVH-detection are made available to groups of African ancestry, particularly in the obese. However, to reduce costs of screening patients with obesity for LVH using alternative techniques such as echocardiography it may be useful to develop an algorithm that allows clinicians to identify those patients whom are most likely to have LVH and hence warrant echocardiography. This algorithm would be expected to be most effective if all possible clinically determined variables are incorporated into the algorithm. To identify these variables, it is first necessary to consider those factors that may explain significant variations in LVM at a population level and identify those that may be of importance in groups of African ancestry. The question that arises at this point in the discussion is, what are the possible mechanisms that may explain the excessive LVH that occurs in groups of African ancestry?

1.3.1 Possible mechanisms that could explain the high prevalence of left ventricular hypertrophy in groups of African descent.

Although there is no question that a higher prevalence of conventional risk factors such as hypertension and obesity, account for a significant proportion of the increased LVM in Africans as compared to Caucasians, there are a number of additional mechanisms that could also explain a high prevalence of LVH. In the following sections, I

will first discuss the haemodynamic factors that influence the development of increased LVM that may not be routinely available for clinical assessment (section 1.3.1.1), then the evidence in favour or against some non-haemodynamic factors (section 1.3.1.2) as possible mechanisms responsible for LVH and the increased prevalence of LVH in Africans as compared to Caucasians. In this regard I will focus on those factors that were evaluated as possible mechanisms involved in producing LVH assessed in the present thesis. I will not discuss all of the potential non-haemodynamic mechanisms as this goes beyond the scope of the present thesis, but in this thesis I provide novel evidence to show the significant role for early chronic kidney disease and the inflammatory marker C-reactive protein in accounting for variations in LVM independent of haemodynamic factors.

1.3.1.1 Non-conventional haemodynamic factors that may account for variations in left ventricular mass: Important role in groups of African ancestry.

It has been suggested that Africans may have a greater susceptibility to the adverse effects of BP on LVM (Xie et al 1994, Hammond et al 1984, Harris et al 2000), but the mechanisms of these effects have not been identified. Nevertheless, with respect to the determinants of BP, African hypertensives (but not normotensives) have a higher total peripheral resistance (TPR) than Caucasians (Hammond et al 1984). To reduce cardiac loads produced by an excessive increase in TPR, the consequence may be a greater degree of compensatory LV wall thickening (Hammond et al 1984). Indeed, posterior wall thickness may correlate with TPR in Africans but not in Caucasians (Dunn et al 1983).

With respect to BP effects *per se*, a number of possible differences in BP may account for the higher prevalence of LVH in groups of African ancestry as opposed to Caucasians. In this regard, Africans may have an earlier onset of an elevated BP than Caucasians with the consequence being that through temporal effects, compensatory LVH may be 2-3 times higher than in Caucasians (Beaglehole et al 1975). Moreover, one

must consider the possibility that office BP measurements do not closely reflect the effect of BP *per se* on the heart. In this regard, some studies have reported on the superiority of ambulatory over conventional BP with respect to associations with LVM. In the Italian Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation (SAMPLE), a longitudinal study (n = 206), there was no correlation between clinic systolic BP and LVMI at baseline or the change in LVMI and clinic systolic BP over 12 months of antihypertensive treatment (Mancia et al 1997). However, there was a significant correlation between ambulatory (24 hour) systolic BP and LVMI both at baseline and the change in 24-hour systolic BP and LVMI over 12 months of antihypertensive treatment (Mancia et al 1997). Thus regression of LVH due to antihypertensive treatment may be accounted for by ambulatory, but not by clinic systolic BP in some studies (Mancia et al 1997). As groups of African ancestry, through attenuated decreases in BP at night may have higher 24-hour ambulatory BP values for a given office BP (Wang et al 2006), it is possible that differences in ambulatory BP may indeed explain the higher prevalence of LVH in Africans as compared to Caucasians.

Alternative haemodynamic factors may also account for an increased prevalence of LVH in groups of African ancestry. In this regard, indices of aortic stiffness may be associated with cardiovascular damage and outcomes independent of conventional cardiovascular risk factors including office BP (Saba et al 1993, London et al 2001, Nurnberger et al 2002, Hayashi et al 2002, Weber et al 2004, Ueda et al 2004, Weber et al 2005, Chirinos et al 2005, Williams et al 2006, Schillaci et al 2007, Hashimoto et al 2007, Safar et al 2002, Roman et al 2007, Libhaber et al 2008, Wang et al 2009, Rabkin and Chan 2012). Moreover, relationships between central aortic systolic BP and LVMI may occur independent of peripheral systolic BP (Wang et al 2009) and these relationships have been noted in a group of African ancestry (Norton et al 2012). In this regard, an increased sodium intake is associated with increases in indices of aortic stiffness in groups of African descent (Redelinghuys et al 2010) and increases in indices of aortic stiffness have been shown to be associated with LVM in groups of African

ancestry (Libhaber et al 2008). Thus, it is possible that that the higher prevalence of LVH in groups of African ancestry may be attributed to an enhanced aortic stiffness and central aortic BP.

1.3.1.2 Non-haemodynamic factors that may account for variations in left ventricular mass

Even on antihypertensive therapy, therapy which has been shown to decrease TPR, 24-hour BP and indices of aortic stiffness, Africans still have a 13% higher LVM in men and 17% higher LVM in women than Caucasians (Arnett et al 1994). Thus, haemodynamic factors (office BP or other haemodynamic changes) may not adequately explain all variations in LVM. A number of non-haemodynamic factors have been proposed as contributing toward an increased LVM in groups of black African descent. Although there are many non-haemodynamic factors that may account for variations in LVM, in the present thesis I focussed mainly on the possible roles of chronic kidney disease (as determined by the estimated glomerular filtration rate-eGFR) and non-specific inflammation (as determined by C-reactive protein - CRP). Thus, in the following sections I will summarise the evidence to support the view that early alterations in renal function or measures of inflammation are associated with increases in LVM and highlight the evidence that prompted me to further evaluate these relationships in the present thesis.

1.3.1.2.1 Early chronic kidney disease and left ventricular hypertrophy

Importantly, there is some evidence to suggest that groups of African ancestry may have a higher prevalence of impaired renal function (Wachtell et al 2002). In this regard, African Americans were reported to have a four times higher risk of end stage renal disease (ESRD) than Caucasians (Martins et al 2002, Weiner et al 2004, Duru et al 2008). It is therefore possible that early renal dysfunction may contribute toward the higher prevalence of LVH in groups of African ancestry. However, this hypothesis would

only hold true if there was sufficient evidence to suggest that early renal dysfunction indeed contributes toward LVH independent of haemodynamic factors. Hence there should be a strong link between early renal dysfunction and LVH in both hypertensive and normotensive Africans regardless of their diabetic status. This would discount the effects of all the other haemodynamic factors which may influence development of LVH in hypertensives.

A number of studies have established a relationship between renal impairment and left ventricular mass (LVM) long before the development of overt renal failure (Levin et al 1996, Culleton et al 1999, Landray et al 2001, Wachtell et al 2002, Manjunath et al 2003, Leoncini et al 2003, Leoncini et al 2004, Weiner et al 2004, Henry et al 2005, Paoletti et al 2005, Verma et al 2007, Leoncini et al 2008, Grabysa and Cholewa 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata et al 2010, Cioffi et al 2011) independent of conventional BP (Levin et al 1996, Landray et al 2001, Leoncini et al 2003, Leoncini et al 2004, Henry et al 2005, Paoletti et al 2005, Leoncini et al 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata et al 2010, Cioffi et al 2011) and 24 hr BP load (Cerasola et al 2010). Table 1.7 summarises the characteristics and results of these and other studies which suggest that early renal dysfunction results in increases in LVM.

Although associations between early CKD and LVM have consistently been demonstrated to be independent of conventional BP (Levin et al 1996, Landray et al 2001, Leoncini et al 2003, Leoncini et al 2004, Henry et al 2005, Paoletti et al 2005, Leoncini et al 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata et al 2010, Cioffi et al 2011), as outlined in Table 1.7, these studies have largely been conducted in select clinical samples of which 66-100% of participants were either hypertensive or had a history of hypertension. Residual confounding long-term haemodynamic effects produced by hypertension may therefore explain these relations (Levin et al 1996, Landray et al 2001, Leoncini et al 2003, Leoncini et al 2004, Henry et al 2005, Paoletti et al 2005, Leoncini et al 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata

Table 1.7. Summary of studies reporting on the relationship between early renal dysfunction and left ventricular mass. The meaning of abbreviations is given at the end of the Table.

Reference, Setting, Location	Study and period	Ethnicity	n	% ♀	% HTN	Group	Findings
Levin et al 1996; Research Clinic; Canada		Undefined (Caucasian)	175	34.3	-	Renal patients commencing dialysis	LVH prevalence ↑ with ↓ in renal function. A 5 year age ↑ was associated with a 3% ↑ in LVH risk whilst a 10g/L ↓ in haemoglobin was associated with a 6% ↑ in LVH.
Culleton et al 1999; Population based; USA	Framingham Heart Study; 1977 – 1994	Undefined (Caucasian)	6223	54	39.3	Random population sample	A 3 to 4x higher prevalence of LVH was found in participants with mild renal impairment.
Landray et al 2001; Research Clinic; United Kingdom		Undefined (Caucasian)	369	33	76	Patients with mild & patients with chronic renal impairment (CRI)	Mild CRI is associated with vascular disease and the severity is proportional to the severity of renal dysfunction.
Wachtell et al 2002; Multicentre, Population-based; Multinational (Denmark, Finland, Iceland, Norway, Sweden, UK and USA)	Losartan Intervention for Endpoint Reduction (LIFE)	Multiethnic: 13.6% Afr, 84% Cau, 2% Hisp, 0.4% Asian	964	42	100	Hypertensive Patients (Stage I - III)	Hypertensives with eccentric or concentric LVH had a 2x higher prevalence of microalbuminuria. There is a strong association between LVM and UACR independent of diabetes and partly independent of systolic blood pressure. ↑ UACR was strongly related to African race.
Leoncini et al 2003; Research Clinic Based; Genoa, Italy	Microalbuminuria: Genoa Investigation on Complications Study (MAGICS); 1998 – 2001	Undefined (Caucasian)	246	39	100	Untreated hypertensives	Echo LVH was lower in patients with normal renal function (42%) than in patients with mild renal dysfunction (71%). A significant linear trend existed between mild renal dysfunction prevalence and ↑ LVM. Mild renal dysfunction was associated with a 3x higher LVH risk.
Manjunath et al 2003; Multicentre, population based; USA	Atherosclerosis Risk in Communities (ARIC) study;	74.1% Cau, 25.9% AA	15350	54.8	34.6	Middle aged participants	There is significant interaction between LVH and GFR although the method used to define the presence of LVH is insensitive.
Leoncini et al 2004; Research Clinic Based; Genoa, Italy	MAGICS; 1998 – 2001	Undefined (Caucasian)	934	41.8	100	Hypertensives	Mild renal dysfunction regardless of its cause, was associated with ↑ LVMI ($g/m^{2.7}$), and ECG determined LVH

Table 1.7. continued.

Reference, Setting, Location	Study and period	Ethnicity	n	% ♀	% HTN	Group	Findings
Paoletti et al 2005; Research clinic based; Genoa, Italy.		Undefined (Caucasian)	244	32.8	66	Non diabetic CKD patients	Patients with CKD stages 3 and 4 had a higher LVH prevalence (78%) as compared to CKD stages 1 and 2 (51%). LVH is also present in the early stages of renal disease and arterial hypertension is associated with LVH in CKD patients.
Henry et al 2005; Population based; The Netherlands.	Hoorn Study; 1989 – 2000	Caucasian	742	49.7	69	Mixed population (HT, NT, Diabetics & non diabetics)	↓ GFR was significantly associated with ↑ LVM in men after adjustments for confounders but ↓ GFR was not significantly associated with ↑ LVM in women. Arterial stiffness accounted for associations between early CKD and LVM.
Verma et al 2007; Multicentre, international study; Multinational - Australia, United Kingdom, Canada, USA	The VALsartan In Acute myocardial iNfarcTion (VALIANT) Study	Multiethnic 94.7% Cau	603	30.3	56.2	Acute MI patients	↑ LVMI, ↑ LAVI, ↓ EDV were significantly associated with ↓ eGFR even after adjustments. There was a stepwise ↑ in LVH and LVM/EDV ratio and a ↓ ESV (ns) with ↓ eGFR. LVH tends to develop in the earliest phases of all forms of renal disease.
Grabysa and Cholewa 2008; Hospital based; Poland		Undefined (Caucasian)	749	-	100	Hospitalised for hypertension	ECG LVH prevalence was the same in patients with and without CKD, but mean LVMI was higher in patients with CKD.
Leoncini et al 2008; Research Clinic Based; Genoa, Italy	MAGICS; 2001 – 2007	Caucasian	459	36	100	Non diabetic untreated hypertensive patients	Patients with renal damage were older females with ↑ LVH prevalence, ↑ LVM, ↑ SBP, ↑BMI and unfavourable cardiac geometries.
Nardi et al 2009; Research Clinic based; Italy		Undefined (Caucasian)	293	-	100	Hypertensive patients	LVH prevalence was high in CKD patients. Patients with CKD had a higher prevalence of LVM_{inappr} and the ↑ LVM was mainly due to ↑ PWT.
Leoncini et al 2009; Research Clinic Based; Genoa, Italy	MAGICS; 2002 – 2007	Caucasian	400	35	100	Non diabetic untreated hypertensives without severe obesity	Patients with renal abnormalities (microalbuminuria or ↓ creatinine clearance) also had higher LVMI, higher prevalence of unfavourable geometric patterns and LVH.

Table 1.7. continued.

Reference, Setting, Location	Study and period	Ethnicity	n	% ♀	% HTN	Group	Findings
Cerasola et al 2010; Research Clinic Based; Italy	Renal Dysfunction in Hypertension (REDHY) Study	Undefined (Caucasian)	455	46	100	Non diabetic hypertensives	↓ renal function is strongly and progressively related to LVH prevalence and ↑ LVM, but adjustment for 24 hr BP in hypertensives left a trend ($p<0.05$) for the relationship between early CKD and LVM. Hence LVM is inversely related to GFR independent of 24 hr BP load.
Masugata et al 2010; Hospital based; Japan		Undefined	309	-	100	Patients with cardiovascular risk factors	eGFR was independently associated with LVMI and hypertension in patients with cardiovascular risk factors.
Cioffi et al 2011; Research Clinic Based; Italy		Undefined (Caucasian)	340	-	-	CKD patients	A ↓ GFR was associated with an ↑LVMinappr, ↑ RWT, diabetes and ↑ maximal left atrial volume. LVM_{inappr} prevalence progressively and significantly ↑ with development of CKD from stage 1 (31%) to stage 5 (100%).

Cau – Caucasian; AA – African American; Afr – African; Hisp – Hispanic; CKD – Chronic kidney disease; ↑ - increased; ↓ - decreased; LVM – Left ventricular mass; LVMI – Left ventricular mass index; EDV – End diastolic volume; ESV – End systolic volume; LAVI – Left atrial volume index ;; SBP – Systolic blood pressure; BP – Blood pressure; GFR – Glomerular filtration rate; eGFR – Estimated glomerular filtration rate; CAD – Coronary artery disease; ns – not statistically significant; PWT – Posterior wall thickness; LVM_{inappr} – Inappropriate left ventricular mass; RWT – Relative wall thickness; TOD – Target organ damage; Urinary albumin-to-creatinine ratio; HT – Hypertensive; HTN – Hypertension; NT - Normotensive.

et al 2010, Cioffi et al 2011). Moreover, arterial stiffness has been reported to account for associations between early CKD and LVM (Henry et al 2005)(Table 1.7). an effect that could be attributed to the impact of increases in arterial stiffness on aortic BP. In this regard, as previously indicated, aortic BP is associated with LVM beyond brachial BP (Wang et al 2009, Norton et al 2012). Furthermore, with adjustments for 24-hour BP, only a trend ($p<0.05$) for a relationship between early CKD and LVM in hypertensives persisted (Cerasola et al 2010)(Table 1.7). In this regard, as also previously indicated, it is well-recognised that 24-hour BP may be more closely associated with LVM than conventional BP (Mancia et al 1997, Mancia and Parati 2000). It is therefore possible that the relationships between early CKD and LVM may be entirely explained by haemodynamic factors. To caste further light on this issue, in the present thesis I assessed associations between early CKD and LVM in a community rather than in a hypertensive sample, and the extent to which these relations are determined by haemodynamic factors. These data and the implications thereof are discussed in chapter 4 of the present thesis and have also been published in the *Journal of Hypertension* (Maunganidze et al 2013b).

1.3.1.2.2 Could the detection of early chronic kidney disease be employed to improve on the ability to identify left ventricular hypertrophy?

As in chapter 4, I was able to show that even very early decreases in eGFR are associated with LVM independent of a number of haemodynamic factors, the obvious question that arises is whether very early decreases in eGFR may be employed to improve on the ability to detect LVH? If so, this would allow for an enhanced ability to identify that obese patient whom may require echocardiography for LVH detection. Hence, in the present thesis I subsequently evaluated whether the use of very early changes in eGFR improves the ability to detect LVH in obesity. These data and the implications thereof are discussed in chapter 6 of the present thesis

1.3.1.2.3 Systemic inflammation and left ventricular hypertrophy

Low grade inflammation, as indexed by increases in C-reactive protein (CRP) concentrations, predict cardiovascular events beyond traditional risk factors (Ridker 2001, Ridker 2003a, Ridker et al 2003b, Bisoendial et al 2010). Indeed, CRP may have a causal role to play in coronary heart disease and ischaemic heart failure. As such CRP is currently available as one clinical marker for risk prediction. Human CRP (a 92kDa protein synthesised by the liver) binds a number of ligands dependent on the presence of calcium. It has a high affinity for phosphocholine residues, extrinsic ligands (including glycan, phospholipids, somatic and capsular components of many parasites, bacteria, fungi and plant products), autologous ligands (including modified or native plasma lipoproteins, apoptotic cells, small nuclear ribonucleoprotein particles and damaged cell membranes) and cellular particulate precipitates or aggregates (Hirschfield and Perpys 2003). A number of studies have demonstrated that low grade inflammation, as indexed by circulating CRP concentrations, is associated with LVM or LVH (Palmieri et al 2003, Pedrinelli et al 2004, Kim et al 2005, Tsioufis et al 2005, Conen et al 2006, Mehta et al 2007, Cottone et al 2007, Salles et al 2007, Iwashima et al 2007, Assadi et al 2007, Ratto et al 2007, Assadi et al 2008, Fertin et al 2010, Takahashi et al 2010, Shi et al 2010, Masugata et al 2011, Arnett et al 2011, Torun et al 2012, Monfared et al 2013). Table 1.8 summarises the essential characteristics of these studies.

C-reactive protein concentrations have been associated with LVM or LVH in the general population (Mehta et al 2007, Arnett et al 2011), in type II diabetes mellitus (Palmieri et al 2003), in hypertensives (Pedrinelli et al 2004, Conen et al 2006, Iwashima et al 2007, Assadi et al 2007, Ratto et al 2007, Assadi et al 2008, Masugata et al 2011, Torun et al 2012), in resistant hypertensives (Salles et al 2007), in patients hospitalised for myocardial infarction (Fertin et al 2010), in end-stage renal disease (Kim et al 2005, Monfared et al 2013), and in systemic lupus nephritis (Shi et al 2010). However,

Table 1.8. Summary of studies reporting on the relationships between CRP and left ventricular mass. The meaning of abbreviations is given at the end of the Table.

Reference, setting, location	Study and period	Ethnicity	n	% Female	Group	Findings
Palmieri et al 2003; Multicentre, Population based; USA	The Strong Heart Study; 1989 – 1995	Undefined	1299	69.7	Random population sample	In type II diabetics, echocardiographic LVH was associated with generally higher hsCRP, fibrinogen and albumin/creatinine ratio. However, the hsCRP/LVH relationship was not statistically significant due to the confounding effect of ↑ BMI .
Pedrinelli et al 2004; Research Clinic Based; Italy	2000 – 2003	Caucasian	220	0	Essential hypertensive Caucasian men	The combination of microalbuminuria and subclinical inflammation evidenced by CRP identifies the high risk patient with a much higher LVH prevalence in essential hypertensives with both high CRP and high microalbuminuria.
Kim et al 2005; Research Clinic; Korea		Undefined	52		Haemodialysis patients	High CRP may predict cardiac hypertrophy and dysfunction in haemodialysis patients.
Tsioufis et al 2005; Research clinic based; Greece		Undefined	65	59	Essential hypertensives	There is an association between alterations in LV geometry (RWT but not LVMI) and ↑ serum CRP levels in essential hypertension patients
Conen et al 2006; Research Clinic based; Switzerland		Undefined (Caucasian)	320	48	Hypertensive patients	In hypertensive patients, CRP (sensitivity = 68% and specificity = 59%) and BNP (sensitivity = 73% and specificity = 72%) concentrations (combined negative predictive value = 99%) determined from a single blood test can be used to exclude or diagnose LVH.
Mehta et al 2007; Population based; USA	Dallas Heart study	Multiethnic (Cau = 33%, Afr = 49%, Hisp = 18%)	2633	55	Random population sample	There is an association between LVH and CRP although the relationship seems to be mediated by comorbid conditions since there was no relationship after multivariate analysis.

Table 1.8. continued.

Reference, setting, location	Study and period	Ethnicity	n	% Female	Group	Findings
Cottone et al 2007; Research Clinic Based; Italy		Undefined	64 CKD 55 EHT		CKD and essential hypertensive patients	hs-CRP and SBP were independent predictors of LVMI in CKD patients.
Salles et al 2007; Research Clinic Based; Brazil	2000 – 2006	Undefined	463	72.2	Resistant hypertension patients	There is an independent association between LVH and ↑CRP levels. There is an association between LVH and both CRP (systemic inflammation) and microalbuminuria – (representing endothelial damage)
Iwashima et al 2007; Hopsital based; Japan	1997 - 2004	Undefined	629	50.9	Essential hypertensive patients	CRP concentration was independently and linearly associated with LVMI and it can aid in refining CVD risk stratification. (Adjustments were for age, sex, diabetes mellitus, SBP and HDL-cholesterol)
Assadi et al 2007; Hospital based; USA	2003 - 2005	Multiethnic (Cau = 15%, AA = 67%, Hisp = 18%)	48	45	Untreated hypertensive children and adolescence	There was a significant association between high CRP levels and LVH in essential hypertensive children. Hydrochlorothiazide (ACEI) therapy had a BP and plasma CRP lowering effect.
Ratto et al 2007; Research clinic based; Italy	2003 - 2006	Undefined	182	32	Untreated primary hypertensives	There was an independent association between hs-CRP and preclinical target organ damage in hypertensives even after adjustments for age, BMI, hypertension duration, smoking habit, BMI, 24hr SBP and DBP, Creat, uric acid, glucose, Trig, LDL-chol and total cholesterol)
Assadi et al 2008; Hospital based; USA	2003 - 2005	Multiethnic (Cau = 15%, AA = 63%, Hisp = 22%)	64	48.4	Essential hypertensive children and adolescence	CRP is as strongly associated with LVH as MA is with LVH in essential hypertensive children and adolescents even after adjusting for age, sex, BMI, DBP, SBP and SBP index.
Fertin et al 2010 Multicentre, Hospital-based study; France	Remodelage Ventriculaire–2 (REVE-2); 2006 – 2008	Undefined	246	19	Hospitalised MI patients	There was a significant relationship between left ventricular remodelling and CRP levels.

Table 1.8. continued.

Reference, setting, location	Study and period	Ethnicity	n	% Female	Group	Findings
Takahashi et al 2010 Research Centre; Japan		Animal study	122		Transgenic mice	Increased CRP expression was associated with LV dysfunction and LV remodelling. There was greater hypertrophy and LV dilatation in mice expressing human CRP implicating the protein in the deliterious effects of inflammation on cardiomyocytes.
Shi et al 2010 Research clinic-based; China	2005 – 2008	Undefined (Chinese)	61	91.3	Lupus nephritis (LN) patients	Serum hs-CRP level is independently correlated with LVMI hence measurement of hs-CRP may provide important clinical information to investigate LVH in LN patients.
Masugata et al 2011 Research hospital; Japan	2008 – 2010	Undefined (Japanese)	185	51.9	Hypertensive, diabetic, or dyslipidaemia patients	Hs-CRP is related to LVH although it has a stronger relationship with LV diastolic dysfunction.
Arnett et al 2011; Population based; USA	Multi-Ethnic Study of Atherosclerosis (MESA);	Multiethnic (Cau = 39.2%, Afr = 25.7%, Hisp = 22.1%, Chinese = 13.1%)	4973	52.3	Random population sample (Asymptomatic for CVD)	The association between CRP and LVM was attenuated by adjusting for traditional cardiovascular risk factors, demographic characteristics, diabetes treatment, hypertension and statin use but a negative relationship emerged between CRP and LVM after adjusting for weight, hence obesity strongly influences the effects of inflammation on LVM.
Torun et al 2012; Hospital Based; Turkey		Undefined	70	58.6	Untreated essential hypertensives	CRP was positively associated with BMI, DBP, fibrinogen, urinary albumin excretion and LVMI. Obesity control may eliminate the inflammatory state in hypertensives and also hypertension induced end organ damage.
Monfared et al 2013; Hospital based; Iran	2010	Undefined	104	36.5	hemodialysis (HD) patients	hs-CRP and systolic blood pressure are independent predictors of LVM and LVMI in HD patients after adjustments for age, sex, HD duration, antihypertensive treatment and etiology of ESRD.

Cau – Caucasian; AA – African American; Afr – African; Hisp – Hispanic; CKD – Chronic kidney disease; ↑ - increased; BP – Blood pressure; DBP – Diastolic blood pressure; SBP – Systolic blood pressure; GFR – Glomerular filtration rate; ACEI – Angiotensin converting enzyme inhibitor; Trig – Triglycerides; Creat – Creatinine; hs-CRP – high sensitivity C-reactive protein; RWT – relative wall thickness; MA – microalbuminuria; ESRD – End stage renal disease; BNP – Brain natriuretic peptide; DM – Diabetes mellitus; CAD – Coronary artery disease; CVD – Cardiovascular disease; HDL – High density lipoprotein; LDL-chol – low density lipoprotein cholesterol.

relationships reported on in these select clinical samples (Pedrinelli et al 2004, Conen et al 2006, Iwashima et al 2007, Assadi et al 2007, Ratto et al 2007, Assadi et al 2008, Masugata et al 2011, Torun et al 2012, Salles et al 2007, Fertin et al 2010, Kim et al 2005, Shi et al 2010, Monfared et al 2013) may represent the effects of a selection bias. Moreover, the relationships reported on in population studies (Mehta et al 2007, Palmieri et al 2003, Arnett et al 2011) may be attributed to the confounding effects of co-morbidities, including obesity, diabetes mellitus, or hypertension. Indeed, the direct relationships between CRP concentrations and LVH noted in two large population samples (n=2633-4973) was not independent of co-morbidities (Mehta et al 2007, Arnett et al 2011). Furthermore, the relationship between CRP and LVH in an alternative large (n=1299) population sample was only noted in those with type II diabetes mellitus (Palmieri et al 2003). Thus, at present there is uncertainty as to the independent role of CRP in mediating LVH. This uncertainty as to whether CRP may independently promote LVH, prompted me in the present thesis to evaluate whether high sensitivity (hs) CRP concentrations are associated with LVM independent of co-morbidities. These data and the implications thereof are discussed in chapter 4 of the present thesis.

1.3.1.2.4 Could C-reactive protein concentrations be employed to improve on the ability to identify left ventricular hypertrophy?

As indicated in previous sections, it is possible that the ability to detect LVH using ECG criteria is considerably impaired in groups of African ancestry, particularly in those with obesity. The obvious question that arises is therefore whether circulating CRP concentrations may improve the ability to detect LVH? In this regard, several studies have been conducted to assess the diagnostic value of CRP for LVH detection (Pedrinelli et al 2004, Conen et al 2006, Kim et al 2005, Salles et al 2007, Shi et al 2010). Indeed, higher CRP concentrations (CRP > 4.2 mg/L [range: 2.3 – 20.7 mg/L], together with an increased urinary albumin excretion [UAE] > 27 μg/minute [range: 15 – 170 μg/minute]) is

associated with a greater prevalence of LVH (79%) than individuals without renal impairment and low grade inflammation (median CRP = 1.0 mg/L [range: 0.1 – 2.2 mg/L], median UAE = 6 μg/minute [range: 2 – 14 μg/minute], LVH = 58%) (Pedrinelli et al 2004). Moreover, in hypertensive patients attending an outpatient's department (n = 320), blood CRP concentrations were noted to provide a high degree of sensitivity (68%), a relatively low degree of specificity (59%), but with a significant performance (area under the receiver operating curve [AUC] =0.616) for LVH detection (Conen et al 2006). Having demonstrated that CRP is indeed associated with LVM independently of a number of co-morbidities, as part of the present thesis I subsequently considered the possibility that CRP concentrations may improve the ability to detect LVH in obesity. In this regard, the low specificity for LVH detection previously demonstrated (Conen et al 2006) is of concern, as LVH detection for risk assessment, for example with ECG criteria, was originally designed to be very specific. However, there are no studies that have evaluated whether the use of CRP concentrations, when considered together with ECG criteria for LVH detection, can enhace the ability of ECG criteria to detect LVH in groups where ECG criteria alone are inappropriate for LVH detection. Therefore, as described in chapter 6 of the present thesis I subsequently evaluated whether the use of blood CRP concentrations, together with measures of renal function, improve the ability to detect LVH when employed together with ECG criteria in a group of African ancestry. This question is particularly important considering that obesity is associated with higher inflammatory marker concentrations (Heilbronn et al 2001, Kopp et al 2003, Giugliano et al 2004) and as demonstrated in chapters 2 and 3 of the present thesis, none of the current ECG criteria can be recommended for LVH detection in obese individuals of African ancestry. These data and the implications thereof are discussed in chapter 6 of the present thesis

1.4 Summary of problem statements

1) Groups of African descent have a high prevalence of LVH. However, the ability to detect LVH using ECG criteria may be considerably reduced. Moreover, this may be exacerbated by obesity, the prevalence of which is increasing in this ethnic group. However, the extent to which obesity modifies ECG criteria for LVH detection and the impact on the sensitivity, specificity and performance of these ECG criteria for LVH detection in this ethnic group is unknown
2) Although glomerular dysfunction, as determined from estimated glomerular filtration rate (eGFR), is associated with LVM, whether this relationship is independent of the presence of hypertension (residual confounding effects) and a number of haemodynamic changes, is uncertain.
3) Although chronic inflammation, as indexed by circulating C-reactive protein concentrations is associated with LVM, whether this relationship is independent of the presence of co-morbidities, is uncertain.
4) If eGFR and CRP are associated with LVM independent of hypertension, alternative haemodynamic factors and co-morbidities, there is a possibility that eGFR and CRP may be employed to improve on LVH detection in groups of African ancestry.

1.5 Aims

1) To evaluate the extent to which obesity modifies ECG criteria for LVH detection in a group of African descent. This aim was addressed in chapter 2 of the present thesis and has been published in-part in the *Journal of Hypertension* (Maunganidze et al 2013a).
2) To evaluate the impact of obesity on the sensitivity, specificity and performance of ECG criteria for LVH detection in a group of African descent. This aim was

addressed in chapter 3 of the present thesis and has been published in-part in the *Journal of Hypertension* (Maunganidze et al 2013a).

3) To evaluate whether eGFR is associated with LVM in a randomly selected population sample of African descent independent of hypertension and a number of haemodynamic factors. This aim was addressed in chapter 4 of the present thesis and has been published in-part in the *Journal of Hypertension* (Maunganidze et al 2013b).

4) To evaluate whether serum CRP concentrations are associated with LVM in a randomly selected population sample of African descent independent of co-morbidities. This aim was addressed in chapter 5 of the present thesis.

5) To evaluate whether eGFR and serum CRP concentrations may be employed to improve on ECG LVH detection in groups of African ancestry. This aim was addressed in chapter 6 of the present thesis.

CHAPTER 2

Obesity Markedly Attenuates Electrocardiographic Criteria for Left Ventricular Hypertrophy Detection in a Group of African Ancestry.

Published in part: Maunganidze (a) *et al.* *J Hypertens 2013;31:377-383.*

Abstract

Although electrocardiographic (ECG) criteria for the detection of left ventricular hypertrophy (LVH) is not as reliable in groups of African ancestry as other ethnic groups, the extent to which this is exacerbated by obesity is uncertain. I aimed to compare relationships between indices of obesity and ECG criteria with those determined from echocardiograph measures of LV mass index (LVMI) and evaluate the impact of these effects on ECG criteria-echocardiographic LVMI relationships in 661 participants from a community sample of African ancestry with a high prevalence of obesity (43%). Body mass index (BMI) was inversely associated with Sokolow-Lyon (SL) voltage (partial r = -0.28, p<0.0001) and the SL product (partial r = -0.17, p<0.0001) as well as the 12 lead QRS voltage sum (partial r = -0.28, p<0.0001) criteria. Moreover, no relationships between BMI and Cornell voltage or product were noted (r=0.04 to 0.07). BMI was associated with voltage criteria that incorporate limb lead recordings only (r=0.14-0.17, p<0.0001), but these relationships were not as strong as BMI-LV mass index (LVMI) relations (r=0.30, p<0.01 to <0.0001 for comparisons of r values). In contrast to the weaker direct relationships between BMI and ECG criteria than between BMI and LVMI, all ECG criteria were as strongly directly related to blood pressure as LVMI. No relationships between SL or 12 Lead QRS sum criteria and LVMI were noted. The relationship between RaVL and LVMI was greater than that between SL and Cornell criteria (p<0.05-0.0001). However, the strength of the correlation between RaVL and LVMI was reduced in obese (r=0.28, confidence intervals=0.17 to 0.39, p<0.0001) as compared to non-obese (r=0.39, confidence intervals=0.30 to 0.47, p<0.0001)(p=0.02 for comparison of relations) participants. In conclusion, these data suggest that in groups of African ancestry with a high prevalence of obesity, neither SL nor Cornell criteria should be employed to detect obesity-induced LVH and the impact of criteria that employ limb lead recordings only, may also be considerably decreased in the obese.

2.1 Introduction

Left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular outcomes (Casale et al 1986, Levy et al 1990a, Koren et al 1991, Levy et al 1994, Verdecchia et al 1996, Ghali et al 1998, Devereux et al 2004, Okin et al 2004a) and as such the electrocardiographic (ECG) identification of LVH is recommended by all hypertension guidelines for routine risk prediction. However, there is uncertainty as to the value of ECG criteria for the detection of LVH in the obese (Levy et al 1990b, Devereux et al 1983, Rautaharju et al 1994, Abergel et al 1996, Okin et al 1996a, Okin et al 1996b, Okin et al 2000) and in those of black African ancestry (Vanezis and Bhopal 2008, Jaggy et al 2000). With the increasing prevalence of obesity in groups of black African ancestry and the strong relationship between obesity and the prevalence and incidence of hypertension (Harris et al 2000, Zhu et al 2005) the combined moderating effect of obesity and African ancestry on ECG criteria for LVH detection may have an important impact on risk prediction in these groups.

Previous studies have shown that an increased adiposity is associated with reduced Sokolow-Lyon voltages (Okin et al 2000) and a decreased sensitivity of Sokolow-Lyon voltages for the detection of LVH (Abergel et al 1996, Okin et al 1996a, Okin et al 1996b). In contrast, the sensitivity for the detection of LVH with Cornell voltages may be unaffected by an excess adiposity (Abergel et al 1996, Okin et al 1996a, Okin et al 1996b). Whether the impact of an excess adiposity on the reliability of ECG criteria is exaggerated in groups of African ancestry (Vanezis and Bhopal 2008, Jaggy et al 2000) is nevertheless uncertain. In this regard, ECG criteria for LVH detection have been shown to be less well correlated with LV mass index (LVMI) in African Americans as compared to Caucasians (Crow et al 1995) and the specificity for identifying LVH is reduced (Vanezis and Bhopal 2008). These effects may be attributed to increased ECG amplitudes in groups of African descent (Lee et al 1992, Chapman et al 1999) possibly produced by a decrease in skin conductivity (Krovetz 1994) or a diminished thoracic diameter reducing

the distance from the skin surface to the heart (Walker et al 1972, Ashcroft 1972, Horton et al 1977). As the effect of obesity on voltage criteria for the detection of LVH in groups of African ancestry has not previously been assessed, in the present study I aimed to evaluate this question in a community sample of black African ancestry with a high prevalence of obesity and hypertension. In the present chapter of this thesis I compared relationships between indices of obesity and ECG criteria for LVH detection with those determined from echocardiographic measures of LVMI; and evaluated the impact of these effects on ECG criteria-echocardiographic LVMI relationships.

2.2 Methods

2.2.1 Study Participants

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval numbers: M020472 renewed as M070469, M1204108 and M10345). Participants gave informed, written consent. The study design has previously been described in a number of publications (Maseko et al 2006, Norton et al 2008, Norton et al 2009, Woodiwiss et al 2008, Woodiwiss et al 2009, Redelinghuys et al 2010, Norton et al 2012, Michel et al 2012). Nuclear families of black African descent mainly from the Nguni (Zulu, Xhosa, Ndebele, Swati), Sotho (South, North Sotho and Tswana) and Venda chiefdoms older than 16 years, with at least one sibling, living in households from formal dwellings were randomly recruited from the South West Township (SOWETO) of Johannesburg. Street names and addresses of households from formal dwellings represented in the 2001 census were obtained from the Department of Home Affairs**.** These households were allocated numbers and numbers were selected from a random number generator. People residing in informal dwellings or institutions/homes were not recruited. No subjects of mixed, Asian, or European ancestry

were recruited and no Khoi-San subjects were recruited. Of the 620 households approached, nuclear families from 351 households agreed to participate (56.6%). Of the 1191 participants recruited, in a substudy consisting of 678 participants, 661 had all echocardiographic and ECG data required for the present analysis.

2.2.2 Clinical, demographic, and anthropometric measurements

Demographic and clinical data were obtained using a standardised questionnaire as previously described (Norton et al 2008, Woodiwiss et al 2008, Woodiwiss et al 2009, Redelinghuys et al 2010, Norton et al 2012, Michel et al 2012). In order to avoid translational errors, the questionnaire was not translated into an African language, but study assistants familiar with all languages spoken in SOWETO and who either previously lived in SOWETO or currently reside in SOWETO assisted with the completion of each questionnaire. Nevertheless, the majority of participants were reasonably proficient in English. Only same sex assistants were used to assist each family member with the completion of the questionnaire. Assistance was only provided when requested. Study assistants first visited homes of subjects that agreed to participate in the study in order to familiarise participants with the questionnaire. 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 a second home visit. A pilot study was conducted in 20 participants 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, including the presence of hypertension, diabetes mellitus and kidney disease, previous cardiovascular events, including stroke, myocardial infarction or heart

failure, the presence of angina pectoris, prior and current drug therapy (analgesic, antihypertensive use and glucose lowering agents included), 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. For females, menstrual history, history of pregnancies and oral contraceptive use was evaluated. Most of the questions simply required a "yes"-"no" answer, but understanding was assessed by requesting some short answers. If participants were unable to provide the name of medication taken these were obtained on a second home visit.

Height, weight, waist circumference (WC), and sub-scapular and triceps skin-fold thickness (Harpenden callipers) were measured using standard approaches and participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. Central obesity was defined as an enlarged WC (≥88 cm in women and ≥102 cm in men)(National Cholesterol Education Program (NCEP) expert panel, 2001). Mean skin-fold thickness was calculated as the mean of sub-scapular and triceps skin-fold thickness values.

2.2.3 Blood Collection and Measurements

To identify medical conditions and syndromes, blood samples were collected by an experienced technician on the participant's first visit to the clinic and sent for analysis at the National Health Laboratory Systems (NHLS) of South Africa to ensure result reliability and reproducibility since these laboratories are accredited as having procedures fulfilling all the criteria for "good laboratory practise". A full blood count with a differential count was requested as well as analyses for blood glucose, renal function (urea, creatinine and electrolyte concentrations), liver function (alanine transaminase, [ALT],

gamma glutamyl transferase [GGT], aspartate transaminase [AST], alkaline phosphatase [ALP], total protein, plasma albumin, total bilirubin, conjugated bilirubin and unconjugated bilirubin concentrations), lipid profile (total cholesterol, low density lipoprotein (LDL) cholesterol; high density lipoprotein (HDL) cholesterol and triglyceride (TG) concentrations), and percentage glycated haemoglobin (HbA1c)(Roche Diagnostics, Mannheim, Germany). Diabetes mellitus or abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or a glycated haemoglobin (Roche Diagnostics, Mannheim, Germany) value >6.1% (Bennett et al 2007). Menopausal status was confirmed with measures of follicle stimulating hormone. Dyslipidemia was defined as a total cholesterol>6.5 mmol/l, LDL cholesterol>4.0 mmol/l, HDL cholesterol<1.2 mmol/l in females and HDL cholesterol<1.0 mmol/l in males. An elevated serum creatinine concentration was defined as ≥107 μmol/l for females and ≥115 μmol/l for males.

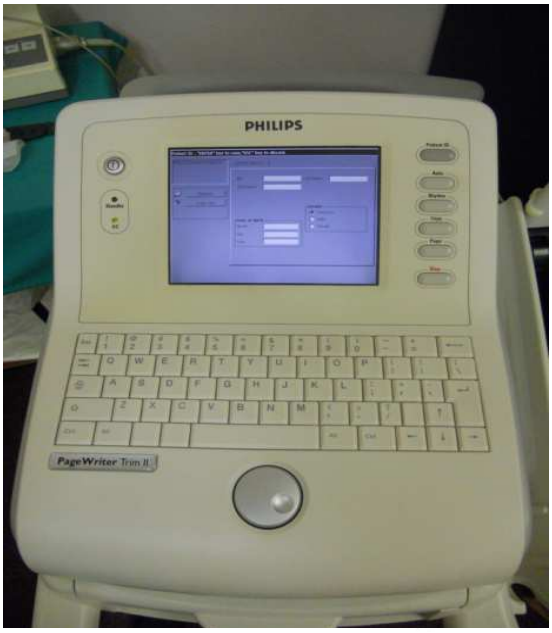
2.2.4 Blood pressure

High quality nurse-derived conventional BP measurements were obtained by a trained nurse-technician according to the European Society of Hypertension and the American Heart Association recommendations using a standard mercury sphygmomanometer (O'Brien et al 2003, Pickering et al 2005). A standard cuff size was employed (22 cm x 12 cm) except in those whose arm circumference exceeded 31 cm when a larger cuff size (31cm x 15 cm) was used. Blood pressure was recorded to the nearest 2 mm Hg. Korotkov phases I and V were employed to identify systolic and diastolic BP respectively and care was taken to avoid auscultatory gaps. Blood pressure was measured 5 times consecutively, at least a minute apart, after the subjects had rested for 5-10 minutes in the sitting position. Blood pressure measurements were obtained between 09:00 and 12:00 hours. The average of the five recordings was taken as the conventional BP. Only 0.7% of visits had fewer than the planned BP recordings.

The frequency of identical consecutive recordings was 0.30% for systolic BP and 0.76% for diastolic BP. The occurrence of BP values recorded as an odd number was 0.02%. Of the systolic and diastolic BP readings, 31.1% ended on a zero (expected =20%). Hypertension was defined as a BP≥140/90 mm Hg or the use of antihypertensive medication.

2.2.5 Electrocardiography

A standard 12-lead ECG was recorded at 25 mm/s and 1.0 mV/cm (Philips, Pagewriter Trim II, Philips Medical Systems, Andover, MA, USA) which allows for computerized information processing, electronic calculations and generation of some interpretive statements based on standard ECG criteria (Figure 2.1). The recordings were interpreted by one trained investigator blinded to the clinical information. R and S wave amplitudes in all leads were measured to the nearest 0.05 mV (0.5 mm). QRS duration was measured to the nearest 4 ms. Measurements of voltage amplitudes were determined using standard approaches. The QRS duration was measured from the beginning of the first downward deflection (Q wave) to the end of the second downward deflection (S wave) (Berbari 2000). Although both the voltage amplitudes of the different waves and the QRS duration were measured in millimeters, the voltage amplitudes were converted to millivolts (mV) using the 10 mm/mV rate, whilst the QRS duration was converted to seconds using the 25 mm/s rate. The distance between the two consecutive R waves (R-R interval) was taken to represent the heart rate (Meek and Morris 2002). The ECG criteria for LVH detection were determined as described in chapter 1, Table 1.2. Before using the cut-off values that were determined in other populations, I analysed a subset of the population which was healthy (i.e. without any history of hypertension, use of lipid lowering drugs, smoking or diabetes mellitus) and the thresholds that I obtained were not significantly different from the cut-off values that had been set in other populations.



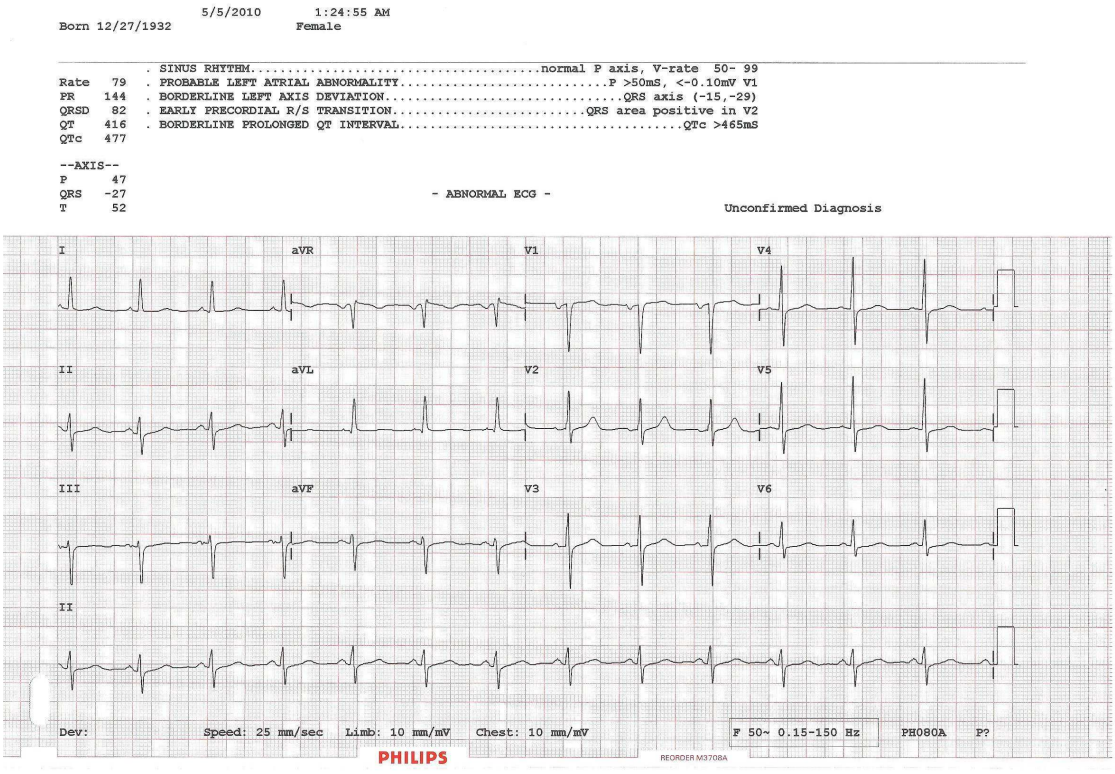


Figure 2.1. The Philips, Page Writer Trim electrocardiogram (ECG)(Philips Medical Systems, Andover, MA, USA) (Top) and sn example of a 12 Lead ECG generated. The ECG trace shows a 2.5 second recording of each of the 12 leads. (Bottom). Computerized information processing by the Philips Page Writer Trim II, enables electronic calculations and generation of some interpretive statements based on standard ECG criteria.

2.2.6 Echocardiography

Echocardiographic measurements were performed using previously described methods on the same echocardiogram (HP-5500, Palo Alto, Ca) (Norton et al 2008, Woodiwiss et al 2008, Libhaber et al 2008, Woodiwiss et al 2009). All measurements were recorded and analyzed by two experienced investigators (CL and AJW) whom were unaware of the clinical data of the participants. All participants were assessed for mitral valve abnormalities as determined using 2-dimensional and color Doppler imaging. Left ventricular (LV) dimensions were determined using two-dimensional directed M- mode echocardiography in the short axis view and these recordings analyzed according to the American Society of Echocardiography 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. M-mode images were obtained perpendicular to the posterior wall and as close to the mitral leaflet as possible without images of the mitral leaflet appearing. Only M-mode images of acceptable quality were analysed. In this regard, acceptable quality was considered to exist when appropriate visualization of both the right and the left septal surfaces occurred and where the endocardial surface of the septal and posterior wall were clearly visible when imaging at the optimal angle of incidence (perpendicular to the posterior wall) and close to the mitral leaflets. The interventricular septal wall thickness (IVST) at end diastole and end systole, the posterior wall thickness (PWT) at end diastole and end systole and the end diastolic and end systolic internal dimensions of the left ventricle were measured. Figure 2.2 shows a representative M-mode image employed to assess left ventricular mass. Left ventricular (LVM) mass was derived according to an anatomically validated formula (Devereux et al 1986) ($LVM = 0.8 \times [1.04 (LVEDD + IVST + PWT)^3 - (LVEDD)^3] + 0.6g$) and indexed to height$^{2.7}$ (LVM index, LVMI). Left ventricular hypertrophy (LVH) was

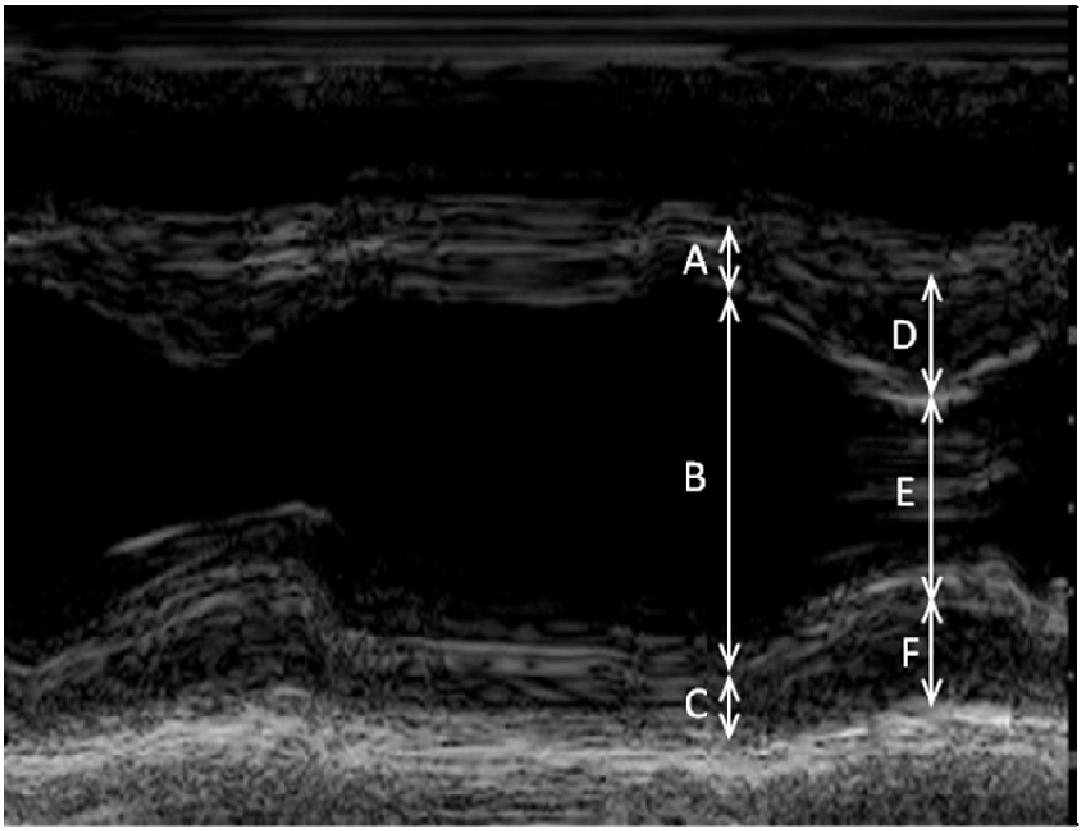


Figure 2.2. A two-dimensional guided M-mode echocardiographic image derived from a Hewlett Packard model 5500 utilised to assess left ventricular dimensions. A, septal wall thickness at end diastole; B, left ventricular end diastolic diameter; C, posterior wall thickness at end diastole; D, septal wall thickness at end systole; E, left ventricular end systolic diameter; F, posterior wall thickness at end systole.

defined as a LVMI >51 g/m$^{2.7}$ for both women and men (Nunez et al 2005). This value was confirmed from the upper 95% confidence interval derived in 140 participants without clinically significant disease and normal clinical blood parameters who were normotensive, non-diabetic, and had a BMI<30 kg/m^2. In these participants the upper 95% confidence interval for LVMI was 51.8 g/m$^{2.7}$.

Intra-observer variability studies were conducted on 29 subjects on whom repeat echocardiographic measurements have been performed within a two week period of the initial measurements. The Pearson's correlation coefficients for LV end diastolic diameter, septal wall thickness and posterior wall thickness were 0.76, 0.94 and 0.89 (all p<0.0001) respectively, and the variances (mean % difference ± standard deviation [SD]) were 0.12±5.95%, -0.77±4.47% and 0.67±5.57% respectively. In addition, no significant differences between repeat measurements were evident on paired t-test analysis (p=0.99, p=0.42 and p=0.48 respectively). Inter-observer variability studies were conducted on 26 participants on whom the two echocardiographers involved in obtaining measurements performed echocardiography on the same participants whilst blinded to each others measurements. The Pearson's correlation coefficients for LV end diastolic diameter, septal wall thickness and posterior wall thickness were 0.96, 0.84 and 0.88 (all p<0.0001) respectively, and the variances (mean % difference ± SD) were 0.49±2.71%, -1.69±7.19% and 0.23±5.89% respectively. In addition, no significant differences between measurements were evident on unpaired t-test analysis (p=0.38, p=0.26 and p=0.85 respectively.

2.2.7 Data analysis

Database management and statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Continuous data are reported as mean ± SD or mean ± standard error of the mean (SEM). Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively.

Independent relations were assessed from multivariate linear regression analysis with appropriate adjustors. Probability values were further adjusted for non-independence of family members using the method of maximum likelihood as implemented by the mixed procedure as defined in the SAS package. Z-Statistics were used to compare correlation coefficients.

2.3 Results

2.3.1 Participant characteristics.

The demographic and clinical characteristics of those with and without echocardiographic and ECG data were similar (Table 2.1). 43% of participants were obese. Of the 43% of participants that were hypertensive, only 35% had controlled BP. 21.8% of participants had LVH (LVMI>51 $g/m^{2.7}$). More women than men were obese (Table 2.2). Obese participants had a higher prevalence of hypertension and diabetes mellitus and higher BP values, LVM, LVMI, and % LVH than non-obese participants (Table 2.2) The % LVH was also greater in overweight (BMI=25.0-29,9 kg/m^2)(20.4%) as compared to normal weight (BMI<25.0 kg/m^2) (7.7%) participants ($p<0.0001$). As compared to normal weight participants, overweight participants also had a higher LVM ($p<0.0005$), and LVMI ($p<0.001$). We were however not statistically powered to separate the participants into lean, overweight and obese groups in some of our analyses, hence for all further analyses we compared non-obese with obese.

2.3.2 Relationships between BMI or BP and either ECG criteria or LVMI.

With sex and systolic BP adjustments, BMI was positively related to RaVL, Gubner-Ungerleider and Lewis voltages, but these relationships were lower than that between BMI and LVMI (Figure 2.3, lower panel). Moreover, BMI was unrelated to Cornell voltage criteria and inversely related to Sokolow-Lyon voltage criteria (Figure 2.3, lower

Table 2.1. Characteristics of study participants with and without echocardiographic data.

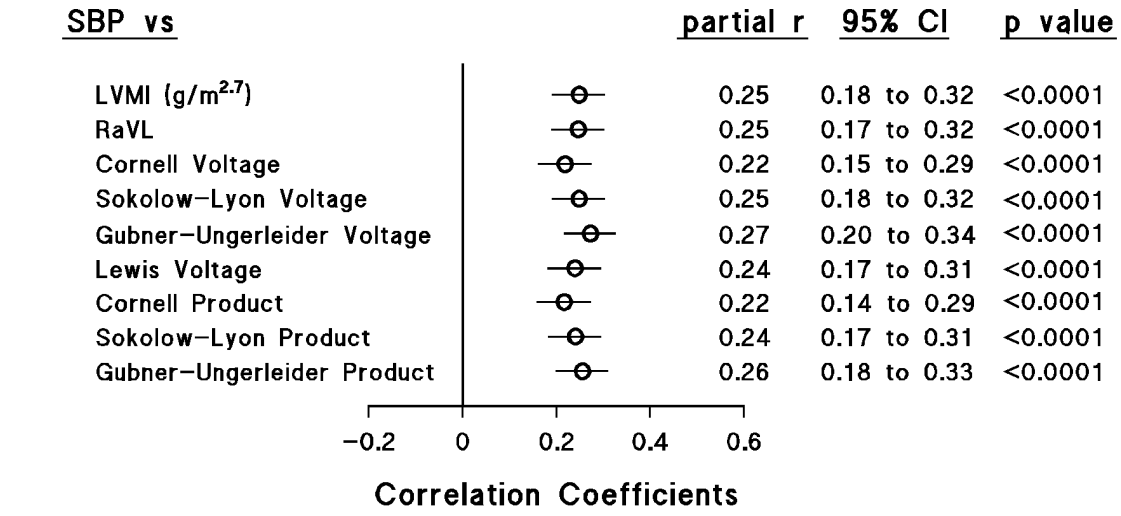
Echocardiography	With	Without
Number (% women)	661 (65.5)	530 (64.9)
Age (years)	43.2±17.8	44.0±18.5
Body mass index (kg/m^2)	29.4±7.8	29.6±8.3
Waist circumference (cm)	90.4±16.6	90.1±16.7
% Overweight/%obese	23.7/43.0	21.9/42.3
% Hypertension	43.1	41.3
% Receiving antihypertensives	24.8	22.8
% Treated for diabetes mellitus	7.9	5.5
% Diabetes mellitus or HbA1c >6.1%	25.1	25.5
% Regular smoking	14.5	15.5
% Regular alcohol	19.8	22.8
Conventional systolic/diastolic BP (mm Hg)	129±22/84±13	130±23/84±13

All continuous data are expressed as mean±SD. BP, blood pressure; HbA1c, glycated haemoglobin.

Table 2.2. Characteristics and electrocardiographic and echocardiographic measures in obese and non-obese participants of African ancestry.

	Non-obese (n=377)	Obese (n=284)
% Female	50.1	85.9**
Body mass index (kg/m^2)	23.9±3.6	36.7±5.5**
% Hypertensive	31.0	59.2**
% with diabetes mellitus or HbA1c>6.1%	13.8	40.1**
Systolic BP/ diastolic BP (mm Hg)	125±21/82±12	135±23/87±13**
Left ventricular mass (LVM) (g)	144.9±45.7	166.7±53.4**
Adjusted† LVM (g)	142.0±47.6	170.5±48.4**
LVM index (LVMI) (g/m$^{2.7}$)	38.6±11.9	47.5±14.6**
Adjusted† LVMI	39.2±13.2	46.7±13.5**
% with LVMI>51 g/m$^{2.7}$	13.0	66.6**
Adjusted† % with LVMI>51 g/m$^{2.7}$	13.0	66.6**
	Voltage criteria	
Sokolow-Lyon (mV)	2.88±0.90	2.41±0.79**
Adjusted† Sokolow Lyon (mV)	2.87±0.85	2.42±0.86**
Cornell (mV)	1.62±0.78	2.06±0.75**
Adjusted† Cornell (mV)	1.76±0.74	1.88±0.76*
RaVL (mV)	0.29±0.30	0.51±0.40**
Adjusted† RaVL (mV)	0.31±0.35	0.48±035**
Gubner-Ungerleider (mV)	0.85±0.51	1.17±0.68**
Adjusted† Gub-Ung (mV)	0.89±0.60	1.11±0.61**
Lewis (mV)	-0.02±0.96	0.62±0.97**
Adjusted† Lewis (mV)	0.07±0.97	0.51±0.99**
	Time-voltage criteria	
Sokolow-Lyon x QRS duration (mV.ms)	247±100	211±86**
Cornell x QRS duration (mV.ms)	143±90	181±86**
Gub-Ung x QRS duration (mV.ms)	74±56	105±71**

Gub-Ung, Gubner-Ungeleider; Sokolow-Lyon=SV_1+RV_5 or V_6; Cornell=RaVL + SV_3(+0.8 mV in women); Gubner-Ungerleider = RI+SIII; Lewis = (RI+SIII)-(RIII+SI). * p<0.05, **p<0.0001 vs non-obese . †Adjusted for sex and conventional systolic blood pressure.



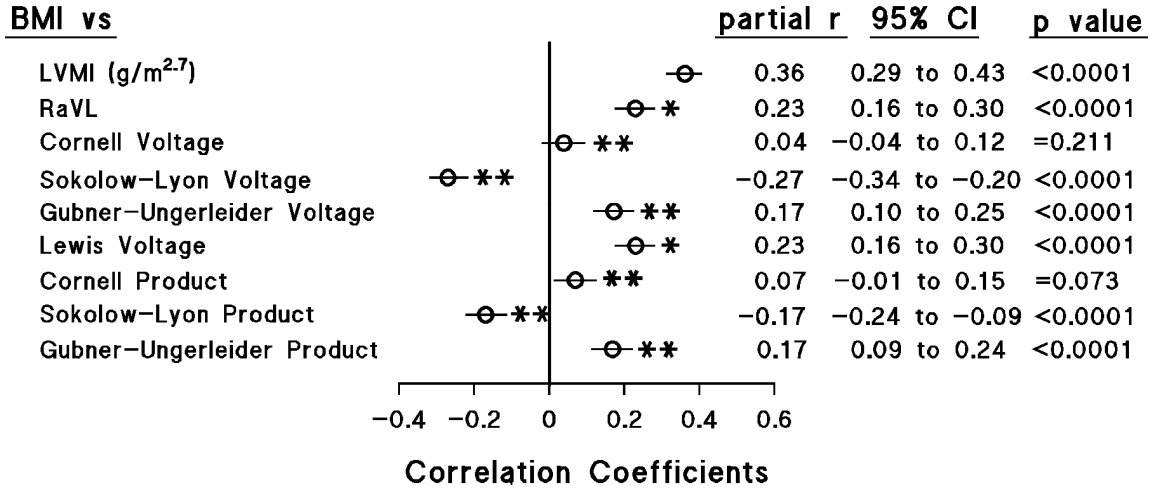


Figure 2.3. Multivariate adjusted relationships between systolic blood pressure (SBP) (upper panel) or body mass index (BMI) (lower panel) and either echocardiographic left ventricular mass indexed to height$^{2.7}$ (LVMI) or electrocardiographic criteria for LV hypertrophy in 661 participants from a community sample of African ancestry. Adjustments are for sex and body mass index. *p<0.01, **p<0.0005 versus BMI-LVMI relationship.

panel). The use of time-voltage products failed to improve on relationships between BMI and ECG criteria (Figure 2.3, lower panel).

2.3.3 Relationships between BP and either ECG criteria or LVMI.

The relationship between sex and BMI-adjusted systolic BP-ECG criteria relationships was similar to that of the relationship between BP and LVMI (Figure 2.3, upper panel). All BP-ECG criteria relationships were similar. The correlation between systolic BP and LVMI was equally as strong in the obese ($r=0.30$, $p<0.0001$) as it was in the overweight and lean ($r=0.29$, $p<0.0001$).

2.3.4. Electrocardiographic criteria in obese versus non-obese participants.

As compared to non-obese participants, both before and after sex and systolic BP adjustments, obese participants had higher ECG voltage criteria that incorporate limb lead recordings only, Cornell voltages, but lower Sokolow-Lyon voltages (Table 2.2) and similar QRS durations (data not shown). As compared to normal weight participants, overweight participants had higher RaVL ($p<0.05$) and Lewis ($p<0.01$) voltages and similar Sokolow-Lyon, Cornell and Gubner-Ungerleider voltages and QRS duration (data not shown).

2.3.5 Explanation for poor direct relationships between BMI or obesity and ECG volltages that incorporate precordial recordings.

The lack of relationship between BMI and Cornell voltages (Figure 2.3, lower panel) and the similarity in Cornell voltages between obese and non-obese participants (Table 2.2) is attributed to the unadjusted ($r=-0.09$, $p<0.05$) and sex and systolic BP-adjusted (partial $r=-0.08$, $p<0.05$) inverse relationship between BMI and SV_3 and the lower SV_3 values in the obese as compared to the non-obese (Figure 2.4). The inverse

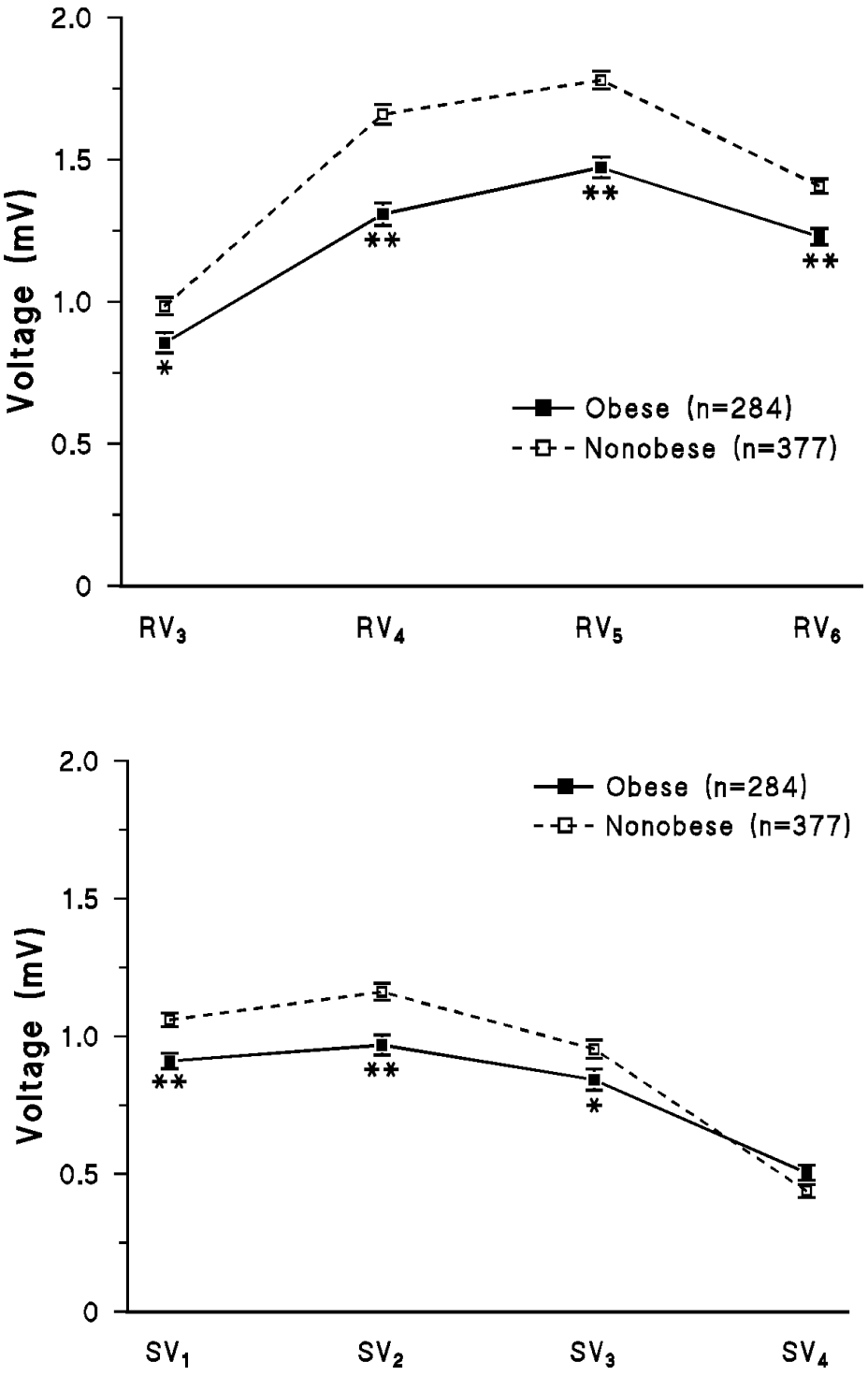


Figure 2.4. Impact of obesity on the amplitude of R (upper panel) and S (lower panel) waves in precordial electrocardiographic leads (V_{1-6}) in 661 participants from a community sample of African ancestry. All data are adjusted for sex and systolic blood pressure. *p<0.05, **p<0.0005 versus non-obese. Data are shown as mean±SEM.

relationships between BMI and Sokolow-Lyon voltages (Figure 2.3, lower panel) and the lower Sokolow-Lyon voltages in obese as compared to non-obese participants (Table 2.2) is attributed to the unadjusted and sex and systolic BP-adjusted inverse relationships between BMI and SV_1 (partial r=-0.16, p<0.0001), RV_5 (partial r=-0.27, p<0.0001) and RV_6 (partial r=-0.18, p<0.0001) and the lower SV_1, RV_5 and RV_6 amplitudes in the obese as compared to the non-obese (Figure 2.4). The sex and systolic BP adjusted inverse relationship between BMI and Sokolow-Lyon voltages was sufficiently strong that it occurred in both obese (partial r=-0.22, p<0.0005) and non-obese (partial r=-0.11, p<0.05) groups. The inverse BMI-Sokolow-Lyon voltage relationship in the non-obese we attribute to the inverse relationship between BMI and RV_5 (partial r=-0.13, p<0.05) and the lack of relationship between BMI and SV_1 (partial r=-0.03, p=0.59) or RV_6 (partial r=-0.05, p=0.36).

2.3.6. Correlations between ECG criteria and LVMI.

Cornell, RaVL, Gubner-Ungerleider and Lewis voltages were correlated with LVMI (Table 2.3). No univariate correlations between Sokolow-Lyon voltages or time-voltage products and LVMI were noted, but with the inclusion of BMI as a confounder, Sokolow-Lyon voltages or time-voltage products were directly correlated with LVMI (Table 2.3). The relations between RaVL and LVMI were greater than those for Cornell or Sokolow-Lyon voltages or time-voltage products and LVMI (Table 2.3). The use of time-voltage products did not improve on relations between Gubner-Ungerleider or Cornell voltages and LVMI (Table 2.3). Although RaVL and alternative criteria that employ limb lead recordings showed the strongest correlations with LVMI, the strength of the correlation was reduced in obese (r=0.28, confidence intervals=0.17 to 0.39, p<0.0001) as compared to non-obese (r=0.39, confidence intervals=0.30 to 0.47, p<0.0001)(p=0.02 for comparison of relations) participants.

Table 2.3 Correlations between electrocardiographic criteria for left ventricular hypertrophy and echocardiographic left ventricular mass indexed to height$^{2.7}$ (LVMI) in 661 participants of a community sample of African ancestry.

LVMI versus	r value*	95% CI	p value
Sokolow-Lyon voltage	-0.05††	-0.13 to 0.02	=0.17
Sokolow-Lyon x QRS duration	0.03††	-0.05 to 0.11	=0.44
BMI-adjusted Sokolow-Lyon voltage	0.10††	0.02 to 0.17	<0.02
BMI-adjusted SL x QRS duration	0.12††	0.04 to 0.19	<0.005
Cornell voltage	0.28†	0.21 to 0.35	<0.0001
Cornell x QRS duration	0.29†	0.23 to 0.36	<0.0001
RaVL	0.38	0.31 to 0.44	<0.0001
Gubner-Ungerleider	0.32	0.25 to 0.39	<0.0001
Gubner-Ungerleider x QRS duration	0.31	0.24 to 0.38	<0.0001
Lewis voltage	0.35	0.28 to 0.41	<0.0001

BMI, body mass index; SL, Sokolow-Lyon. * Pearson's correlation coefficient. $^{\dagger}p<0.05$, $^{\dagger\dagger}p<0.0001$ versus r value for correlation between RaVL and LVMI.

2.4 Discussion

The main findings of the present study are as follows: In a community sample of African ancestry with a high prevalence of obesity (43%), despite the strong independent relations noted between BMI and LVMI, BMI was not associated with Cornell voltages; BMI was inversely associated with Sokolow-Lyon voltages; and the relationship between BMI and ECG criteria that employ limb lead recordings was attenuated. In contrast, relationships between BP and ECG criteria for LVH detection were just as strong as those between BP and LVMI. The poor direct relationships between BMI and Sokolow-Lyon and Cornell criteria were attributed to a marked attenuation of the amplitude of precordial lead QRS complexes in obese participants. Moreover, although the strongest relationships between ECG criteria for LVH detection and LVMI were noted for criteria which employ limb lead recordings only, these relationships were also attenuated by the presence of obesity.

It is uncertain to what extent Cornell voltage criteria are diminished by obesity. Previous studies have demonstrated that the individual components of the Cornell voltage criteria (RaVL and SV_3) increase with body weight (Rautaharju et al 1994), and that Cornell voltage criteria increase with BMI (Okin et al 2000). However, whether these increments in Cornell voltages in association with obesity are in-part attenuated by the inclusion of SV_3, a precordial recording which may be decreased by obesity is unknown. In the present study conducted in a randomly selected community sample of African ancestry with a high prevalence of obesity, I show that although RaVL may be positively associated with BMI, SV_3 is inversely associated with BMI and this effect is sufficiently large that Cornell voltages (the sum of RaVL and SV_3) may be unrelated to BMI. Potential explanations for the differences between the present and prior studies (Rautaharju et al 1994, Okin et al 2000) include the low prevalence of obesity in one prior study (Rautaharju et al 1994) and the use of hypertensive patients with electrocardiographic evidence for LVH in an alternative study (Okin et al 2000), an effect that may have

potentiated the positive impact of BMI on Cornell voltage criteria. Importantly however, the impact of the incorporation of SV_3 into criteria for LVH detection, such as employed in the Cornell voltage or product criteria, in communities with a high prevalence of obesity, is highlighted by the reduced relationship between Cornell voltages or product and echocardiographically-determined LVMI in comparison to that noted between RaVL alone and echocardiographically determined LVMI.

Previous studies have demonstrated a negative relationship between Sokolow-Lyon voltage criteria and BMI (Okin et al 2000) possibly through an attenuation of the amplitude of the R wave in V_5 (Rautaharju et al 1994). In the present study I provide strong support for inverse relationships between BMI and Sokolow-Lyon criteria mediated by decreases in SV_1, SV_5 and SV_6. This occurred despite the strong direct relationship noted between BMI and echocardiographic LVMI. The lack of relationship between Sokolow-Lyon criteria and LVMI is likely to be attributed to the impact of obesity on precordial lead amplitudes and is reminiscent of the poor relationships noted between Sokolow-Lyon criteria and LVMI in the Framingham study (r=0.05-0.069) (Norman et al 1995) where a higher prevalence of overweight or obesity may have occurred in comparison to alternative studies.

Prior studies have not reported on the impact of obesity on ECG criteria that employ limb lead recordings. Although BMI was directly correlated with RaVL and alternative ECG criteria that employ limb lead recordings alone (Gubner-Ungerleider and Lewis), the strength of these relations was lower than that for BMI and LVMI. This was despite the equally strong relationships noted between BP and either these ECG criteria or echocardiographic LVMI. In addition the correlation coefficients for relationships between RaVL or alternative criteria that employ limb lead recordings only and LVMI was reduced in obese as compared to non-obese participants. Thus, it is possible that an excess adiposity is also associated with an attenuation of criteria that employ voltages in limb lead recordings alone.

In conclusion, the present study shows that in groups of African descent an excess adiposity considerably attenuates the amplitude of ECG precordial lead recordings. Consequently, this markedly reduces the relationships between BMI and ECG criteria for LVH detection that employ precordial lead recordings and the relationship between these ECG criteria and echocardiographic LVMI. Moreover, obesity diminishes the relationships between ECG criteria that employ limb lead recordings only and echocardiographically-determined LVMI. These findings question the utility of employing ECG criteria for obesity-associated LVH detection in groups of African ancestry. The impact of obesity on the sensitivity, specificity and performance of ECG criteria for LVH detection in this ethnic group requires further consideration.

CHAPTER 3

Validity and Performance of Electrocardiographic Criteria for Left Ventricular Hypertrophy Detection in a Population of African Ancestry with a High Prevalence of Obesity.

Published in: Maunganidze (a) *et al.* *J Hypertens 2013;31:377-383.*

Abstract

Although electrocardiographic (ECG) criteria for the detection of left ventricular hypertrophy (LVH) is not as reliable in groups of African ancestry as other ethnic groups, the extent to which this is exacerbated by obesity is uncertain. In 661 participants from a community sample of African ancestry, of whom 43% were obese, I evaluated the impact of obesity on the sensitivity, specificity and the overall performance (area under the receiver operating curve [AUC]) of ECG criteria to detect echocardiographically-determined LVH. 21.8% of participants had LVH (LVMI>51 g/$m^{2.7}$). Although Sokolow-Lyon (SL) voltages and time-voltage product criteria and Cornell voltage criteria showed a significant performance for LVH detection in the non-obese, they failed to show a significant performance in the obese (AUC for voltages SL=0.52±0.04, Cornell=0.56±0.04). The performance of SL and Cornell criteria was decreased in the obese as compared to the non-obese ($p<0.05$). ECG criteria which employ limb-lead recordings only (e.g. RaVL) showed a reduced performance in the obese (AUC=0.59±0.04, $p<0.0001$) as compared to the non-obese (AUC=0.75±0.04, $p<0.0001$) ($p<0.005$ for comparison) and a markedly reduced specificity for LVH detection in the obese (76%) than the non-obese (92%, $p<0.0001$) despite similar sensitivities (32% vs 30%). Similar differences in performance, sensitivity and specificity for LVH detection were noted for alternative criteria that employ limb lead recordings only. These findings were largely reproduced in sensitivity analysis conducted in groups with or without diabetes mellitus or a poor blood glucose control. In conclusion, in groups of African ancestry, none of the current ECG criteria for LVH detection can be recommended for use in obesity.

3.1 Introduction

Left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular outcomes (Casale et al 1986, Levy et al 1990a, Koren et al 1991, Levy et al 1994, Verdercchia et al 1996, Ghali et al 1998, Devereux et al 2004, Okin et al 2004) and as such the electrocardiographic (ECG) identification of LVH is recommended by all hypertension guidelines for routine risk prediction. However, there is uncertainty as to the value of ECG criteria for the detection of LVH in the obese (Levy et al 1990b, Devereux et al 1983, Rautaharju et al 1994, Abergel et al 1996, Okin et al 1996a, Okin et al 1996b, Okin et al 2000) and in those of black African ancestry (Vanezis and Bhopal 2008, Jaggy et al 2000). With the increasing prevalence of obesity in groups of black African ancestry and the strong relationship between obesity and the prevalence and incidence of hypertension (Harris et al 2000, Zhu et al 2005), the combined moderating effect of obesity and African ancestry on ECG criteria for LVH detection may have an important impact on risk prediction in these groups.

Irrespective of ethnic origins, previous studies generally agree that an increased adiposity is associated with reduced Sokolow-Lyon voltages (Okin et al 2000, Maunganidze et al 2013a, chapter 2) and as a consequence a decreased sensitivity of Sokolow-Lyon voltages for the detection of LVH (Abergel et al 1996, Okin et al 1996a, Okin et al 1996b). In contrast, an excess adiposity has been reported to be associated with increased Cornell voltages in studies where the dominant ethnic group was Caucasian (Okin et al 2000). However, an absence of relationships between indices of an excess adiposity and Cornell voltages have been noted in a group of African ancestry (Maunganidze et al 2013a, chapter 2). Thus, although in some populations the sensitivity for the detection of LVH with Cornell voltages may be unaffected by an excess adiposity (Abergel et al 1996, Okin et al 1996a, Okin et al 1996b), whether the same holds true for groups of African descent is uncertain. Furthermore, although body mass index (BMI) is directly correlated with RaVL and alternative ECG criteria that employ limb lead

recordings alone (Gubner-Ungerleider and Lewis), the strength of these relations in groups of African descent may be lower than that for BMI and LVMI (Maunganidze et al 2013a, chapter 2). In addition, in a group of African descent the correlation coefficients for relationships between RaVL or alternative criteria that employ limb lead recordings only and LVMI are reduced in obese as compared to non-obese participants (Maunganidze et al 2013a, chapter 2). Thus, there is question as to whether the validity and performance of the use of all current ECG criteria for LVH detection may be impaired by obesity in groups of African descent. In the present study I therefore aimed to determine the effect of obesity on the sensitivity, specificity and performance of ECG criteria for LVH detection in a group of African descent with a high prevalence of obesity.

3.2 Methods

3.2.1 Study participants

The recruitment of study participants is described on pages 56 to 57 in section 2.2.1 of chapter 2 of the present thesis.

3.2.2 Clinical, demographic, and anthropometric measurements

Clinical and demographic data were obtained using a standardised questionnaire as described on pages 57 to 58 in section 2.2.2 of chapter 2 of the present thesis. Anthropometric data was obtained also as described on pages 57 to 58, in section 2.2.2 of chapter 2 of the present thesis. Obesity was defined as a BMI ≥ 30 kg/m^2.

3.2.3 Blood collection and analysis

Blood analysis was performed as described on pages 58 to 59 in section 2.2.3 of chapter 2 of the present thesis.

3.2.4 Conventional blood pressure

Conventional (brachial) blood pressure (BP) measurements were performed as described on pages 59 to 60 in section 2.2.4 of chapter 2 of the present thesis.

3.2.5 Electrocardiography

A standard 12-lead ECG was recorded using the Philips, Pagewriter Trim II, as described on pages 60 to 61 in section 2.2.5 of chapter 2 of the present thesis. All the ECG criteria for LVH were calculated using standard formulae. As groups of black African descent show differences in R and S wave amplitudes as compared to other ethnic groups (Lee et al 1992, Chapman et al 1999), thresholds (cut-points) of ECG criteria for LVH were determined from the upper 95% confidence intervals derived in 140 participants without clinically significant disease and normal clinical blood parameters who were normotensive, non-diabetic, and had a BMI<30 kg/m^2.

3.2.6 Echocardiography

Echocardiographic measurements were performed using two-dimensional targeted M-mode echocardiography as described on pages 62 to 64 in section 2.2.6 of chapter 2 of the present thesis. Thresholds for an increased LVMI are described on pages 62 to 64 in section 2.2.6.

3.2.7 Data analysis

Statistical analysis and database management were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). Continuous data are reported as mean ± SD or mean ± SEM. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. The performance of each of the different ECG criteria for LVH detection was compared to that of echocardiographic LVH detection. Sensitivity and specificity of ECG criteria for LVH detection were determined using standard approaches. The performance of ECG criteria for LVH detection was determined from the area under the receiver operating characteristic (ROC) curves (area under the curve [AUC]). As diabetes mellitus, through alterations in the myocardial matrix, could account for a reduced sensitivity, specificity or performance for the detection of LVH, sensitivity analysis was conducted in those participants with and without diabetes mellitus or an HbA1c>6.1% separately.

3.3 Results

3.3.1 Participant characteristics.

The clinical and demographic characteristics of the participants with and without echocardiography are given in Table 2.1 on page 66 of chapter 2 of the present thesis. A comparison of the characteristics in obese and non-obese participants is provided in Table 2.2 on page 67 of chapter 2 of the present thesis. A description of the essential characteristics of the study group is provided in section 2.3.1 on page 65 of chapter 2 of the present thesis. As we were not statistically powered to separate the participants into lean, overweight and obese groups in some of our analyses, similar to Chapter 2 we only compared the obese and non-obese groups.

3.3.2 Impact of obesity on the sensitivity and specificity of ECG criteria for the detection of an increased LVMI.

The sensitivity for the detection of LVH of RaVL, Gubner-Ungerleider and Lewis voltages was markedly greater than the sensitivity of either Sokolow-Lyon or Cornell voltage criteria in both obese and non-obese groups (Table 3.1). However, the specificity of RaVL, Gubner-Ungerleider and Lewis voltages was markedly reduced in the obese as compared to the non-obese participants despite similar levels of sensitivity (Table 3.1). The use of time-voltage products failed to improve on the sensitivity, or specificity of any of the ECG criteria for LVH (Table 3.1). The differences in the sensitivity and specificity of ECG criteria for the detection of LVH in obese versus non-obese participants were largely reproduced in those without (Table 3.2) and those with (Table 3.3) diabetes mellitus or an HbA1c>6.1%.

3.3.3 Impact of obesity on the performance of ECG criteria for the detection of an increased LVMI.

Sokolow-Lyon time-voltage product, but not Sokolow-Lyon voltages alone showed a significant level of performance in non-obese participants (Table 3.1, Figure 3.1). However, in the obese neither Sokolow-Lyon time-voltage product, nor Sokolow-Lyon voltages alone showed a significant level of performance (Table 3.1, Figure 3.1). Although a significant performance of Cornell voltage criteria in the non-obese group was noted, in the obese group the performance was abolished (Table 3.1, Figure 3.1). The performance of Sokolow-Lyon and Cornell voltage criteria was decreased in the obese as compared to the non-obese ($p<0.05$). The overall performance for the detection of LVH of RaVL was greater than the performance of either Sokolow-Lyon or Cornell voltage or time-voltage criteria for the detection of an LVH in the non-obese group (Table 3.1, Figure 3.1). However, these differences were abolished in the obese group (Table 3.1, Figure

Table 3.1. Sensitivity, specificity and performance (area under the receiver operating curves-AUC) of electrocardiographic indexes as predictors of left ventricular hypertrophy (left ventricular mass indexed to height$^{2.7}$>51 g/m$^{2.7}$)(LVMI) in body size-specific groups.

	ECG threshold	Sensitivity (%)		Specificity (%)		AUC±SEM	
Increased LVMI vs	(mV)	Non-obese	Obese	Non-obese	Obese	Non-obese	Obese
RaVL	0.73	29	32	92	76†††	0.75±0.04**	0.59±0.04*††
Cornell voltage	3.17	8$^{\#}$	10$^{\#\#}$	97$^{\#}$	93$^{\dagger\#\#}$	0.67±0.04**$^{\#}$	0.56±0.04†
Sokolow-Lyon voltage	4.63	0$^{\#\#}$	0$^{\#\#}$	100$^{\#\#}$	100$^{\#\#}$	0.57±0.04$^{\#\#}$	0.52±0.04
Gubner-Ungerleider voltage	1.50	33	34	92	78†††	0.72±0.04**	0.58±0.04*††
Lewis voltage	1.17	33	35	93	75†††	0.71±0.04**	0.59±0.04*†
Cornell time-voltage product	281	12	12$^{\#}$	96$^{\#}$	93$^{\#\#}$	0.65±0.04**$^{\#}$	0.57±0.04*
Sokolow-Lyon time-voltage product	405	10$^{\#}$	2$^{\dagger\#\#}$	94	95$^{\#\#}$	0.58±0.04*$^{\#\#}$	0.54±0.04
Gubner-Ungerleider time-voltage product	125	27	38	90	76†††	0.72±0.04**	0.58±0.04*††

*p<0.05, ** p<0.0005 indicates significance of AUC, †p<0.05, †† p<0.01, †††p<0.0001 vs non-obese. $^{\#}$p<0.05, $^{\#\#}$p<0.001 vs RaVL.

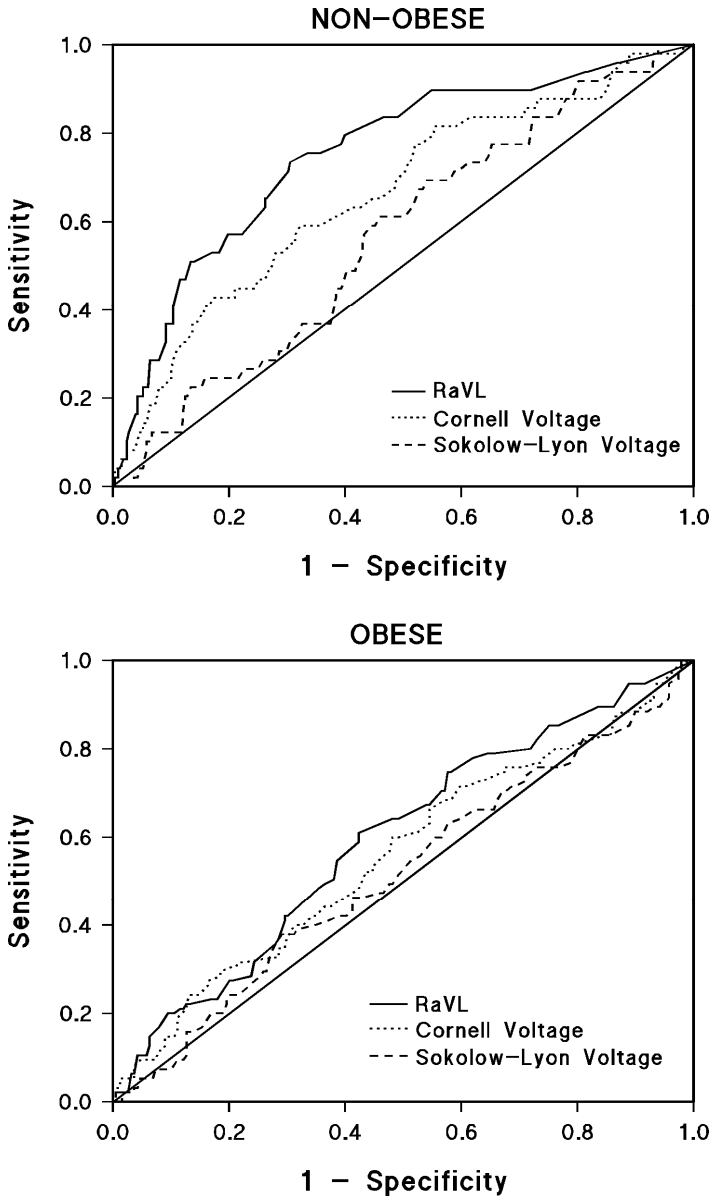


Figure 3.1. Performance of electrocardiographic criteria for left ventricular hypertrophy detection (left ventricular mass index >51 g/m$^{2.7}$) in obese and non-obese participants from a community sample of African ancestry. A comparison of the area under the curves is made in Table 3.1.

3.1). The differences in performance of ECG criteria for the detection of LVH in obese versus non-obese participants were largely reproduced in those without (Table 3.2) and those with (Table 3.3) diabetes mellitus or an HbA1c>6.1%.

3.4 Discussion

The main findings of the present study are as follows: In a community sample of African ancestry with a high prevalence of obesity (43%), obesity was associated with a reduced specificity and overall performance for the detection of LVH of criteria that employ limb lead recordings. Moreover, obesity was associated with a negligible performance of Cornell voltages and Sokolow-Lyon time-voltage criteria.

The results of the present study are in-keeping with alternative studies with small samples of obese participants (n=41-104) (Abergel et al 1996, Okin et al 1996) and in hospital patients (Okin et al 1996) or hypertensives only (Abergel et al 1996) that have demonstrated that obesity is not associated with a decreased sensitivity of Cornell voltage criteria to detect LVH (Abergel et al 1996, Okin et al 1996). However, in the community of African ancestry that I have studied, I show that obesity abolishes the performance of Cornell voltage criteria to detect LVH. This finding that may in-part be attributed to an attenuated BMI-Cornell voltage as compared to the BMI-LVMI relationship described in chapter 2. However, the performance of Cornell voltages for the detection of LVH even in the non-obese was lower than that for RaVL, a finding that may be attributed to the lack of positive relationship between BMI and SV_3 even in the non-obese group as described in chapter 2 and the attenuated relationship between BMI and RaVL as compared to the BMI-LVMI relationship even in the non-obese (see chapter 2). Nevertheless, I cannot exclude the possibility that SV_3 and RaVL in the ethnic group studied may not closely reflect heart size because of a decrease in skin conductivity (Krovetz et al 1994) or a diminished thoracic diameter reducing the distance from the skin surface to the heart (for SV_3)(Walker et al 1972, Ashcroft et al 1972, Horton et al 1977). Irrespective of the explanation for the current

Table 3.2. Sensitivity, specificity and performance (area under the receiver operating curves-AUC) of electrocardiographic indexes as predictors of left ventricular hypertrophy (left ventricular mass indexed to height$^{2.7}$>51 g/m$^{2.7}$)(LVMI) in body size-specific groups in participants without diabetes mellitus or an impaired blood glucose control (HbA1c>6.1%).

	ECG threshold	Sensitivity (%)		Specificity (%)		AUC±SEM	
Increased LVMI vs	(mV)	Non-obese	Obese	Non-obese	Obese	Non-obese	Obese
RaVL	0.73	25	26	93	76†††	0.74±0.04**	0.53±0.05††
Cornell voltage	3.17	5$^{\#\#}$	9$^{\#\#}$	96	94$^{\#\#}$	0.63±0.05*$^{\#}$	0.50±0.05†
Sokolow-Lyon voltage	4.63	0$^{\#\#}$	0$^{\#\#}$	100$^{\#\#}$	100$^{\#\#}$	0.56±0.05$^{\#\#}$	0.51±0.05
Gubner-Ungerleider voltage	1.50	30	26	92	78†††	0.71±0.04**	0.52±0.05††
Lewis voltage	1.17	30	26	93	78†††	0.71±0.04**	0.57±0.05†
Cornell time-voltage product	281	10$^{\#\#}$	11$^{\#\#}$	96	93$^{\#\#}$	0.61±0.05*$^{\#\#}$	0.52±0.05
Sokolow-Lyon time-voltage product	405	10$^{\#\#}$	0$^{\dagger\dagger\dagger\#\#}$	93	95$^{\#\#}$	0.56±0.05$^{\#\#}$	0.47±0.05
Gubner-Ungerleider time-voltage product	125	28	34	90	76†††	0.70±0.04**	0.54±0.05††

Non-obese, n=325; Obese, n=170. *p<0.05, ** p<0.0005 indicates significance of AUC, †p<0.05, †† p<0.01, †††p<0.0001 vs non-obese. $^{\#}$p<0.05, $^{\#\#}$p<0.001 vs RaVL.

Table 3.3. Sensitivity, specificity and performance (area under the receiver operating curves-AUC) of electrocardiographic indexes as predictors of left ventricular hypertrophy (left ventricular mass indexed to height$^{2.7}$>51 g/m$^{2.7}$)(LVMI) in body size-specific groups in participants with diabetes mellitus or an impaired blood glucose control (HbA1c>6.1%).

	ECG threshold	Sensitivity (%)		Specificity (%)		AUC±SEM	
Increased LVMI vs	(mV)	Non-obese	Obese	Non-obese	Obese	Non-obese	Obese
RaVL	0.73	44	37	88	74†	0.78±0.08*	0.63±0.05*
Cornell voltage	3.17	22$^{\#}$	10$^{\dagger\#\#}$	100$^{\#}$	89$^{\dagger\#}$	0.82±0.07*	0.60±0.05*†
Sokolow-Lyon voltage	4.63	0$^{\#\#}$	0$^{\#\#}$	100$^{\#}$	100$^{\#\#}$	0.61±0.11$^{\#}$	0.55±0.06
Gubner-Ungerleider voltage	1.50	44	42	91	79	0.75±0.08*	0.62±0.05*
Lewis voltage	1.17	44	44	91	68††	0.75±0.09*	0.60±0.05*
Cornell time-voltage product	281	22$^{\#}$	13$^{\#\#}$	100$^{\#}$	92$^{\#\#}$	0.84±0.08*	0.61±0.05*†
Sokolow-Lyon time-voltage product	405	11$^{\#\#}$	4$^{\#\#}$	100$^{\#}$	95$^{\#\#}$	0.68±0.11	0.55±0.06
Gubner-Ungerleider time-voltage product	125	22$^{\#\#}$	42††	93	76†	0.80±0.07*	0.63±0.05*†

Non-obese, n=52; Obese, n=114. *p<0.05 indicates significance of AUC, †p<0.05, †† p<0.01, vs non-obese. $^{\#}$p<0.05, $^{\#\#}$p<0.001 vs RaVL.

findings, the present study provides strong evidence to suggest that Cornell voltage or time-volatge product criteria should not be employed to detect LVH in obese individuals from urban, developing communities of African ancestry.

Possibly through an attenuation of voltages in precordial leads, previous studies have demonstrated a reduced sensitivity of Sokolow-Lyon criteria to detect LVH in obesity (Abergel et al 1996, Okin et al 1996a, Okin et al 1996b). In keeping with reduced precordial lead voltages associated with obesity and a lack of relationship between Sokolow-Lyon criteria and LVMI possibly because of the high prevalence of obesity (see chapter 2), in the present study I show that Sokolow-Lyon time-voltage product also showed a reduced sensitivity to detect LVH in the obese as compared to the non-obese (2% vs 10%) and a negligible performance of Sokolow-Lyon time-voltage criteria in the obese. These data therefore also support the notion that Sokolow Lyon voltage or time-voltage product criteria should not be employed to detect LVH in obese individuals from urban, developing communities of African ancestry.

In the present study the specificity and the overall performance for LVH detection of RaVL or alternative criteria that employ limb lead recordings alone was considerably reduced in obese as compared to non-obese participants. This may be explained by the fact that, as indicated in chapter 2, the relationship between BMI and RaVL or alternative ECG criteria that employ limb lead recordings alone (Gubner-Ungerleider and Lewis) was lower than that for BMI and LVMI. Indeed, as also indicated in chapter 2, the correlation coefficients for relationships between RaVL or alternative criteria that employ limb lead recordings only and LVMI was reduced in obese as compared to non-obese participants. Thus, it is possible that an excess adiposity is also associated with an attenuation of criteria that employ voltages in limb lead recordings alone for LVH detection. Importantly, although RaVL and alternative criteria that employ limb lead recordings only did show a significant performance for LVH detection, the very low specificity for LVH detection in the obese (75-78%) precludes the use of these criteria in obesity in groups of African ancestry. In this regard, far too many persons would be labelled as having LVH, whom in fact have no LVH,

whereas ECG criteria for LVH detection were originally designed to be highly specific (>90%) despite having a low degree of sensitivity. Thus, in the absence of access to echocardiography, as is the case in most areas of the public health sector except for large hospitals in South Africa, further work is required to determine whether the specificity of these criteria may be enhanced with alternative measures that are associated with LVH. In this regard, having demonstrated that estimated glomerular filtration rate (eGFR) and high-sensitivity C-reactive protein (hs-CRP) plasma concentrations are independently related to LVMI, in chapter 6 of the present thesis I explored whether eGFR or hs-CRP could enhance the capacity for LVH detection in the community studied.

The limitation of the present study is that there were more females that participated than males. Although sex-specific analyses could be performed in the whole group, the limited number of males with obesity prevented me from evaluating the impact of obesity on the performance of ECG criteria in sex-specific groups. Thus the results of the present study may be specific to females.

In conclusion, as with other studies I show that in a community sample of African ancestry, Sokolow-Lyon criteria have a negligible performance for LVH detection in obesity. However, I extend the results of previous studies by demonstrating that the low level of specificity for RaVL, Gubner-Ungerleider and Lewis criteria, and that the limited performance of the Cornell voltage criterion precludes their use for LVH detection in obese individuals of this ethnic group. Thus, none of the current ECG criteria can be recommended for use in obese people of African ancestry.

CHAPTER 4

Relationship Between Glomerular Dysfunction and Left Ventricular Mass Independent of Haemodynamic Factors in a Community Sample.

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Abstract

Whether relationships between early renal disease and left ventricular mass index (LVMI) are independent of hypertension or haemodynamic alterations is uncertain. In 621 randomly selected participants from a community sample [332 were normotensive (NT)] I aimed to evaluate whether the relationship between estimated glomerular filtration rate (eGFR) and LVM occurs, and whether this relationship depends on haemodynamic factors. LVM and dimensions were determined using echocardiography, and aortic BP assessed from applanation tonometry and SphygmoCor software. Aortic pulse wave velocity (PWV) and high-quality 24-hour BP values were available from 554 and 437 participants respectively. With adjustments for confounders (including clinic systolic BP), eGFR was associated with LVM index (LVMI) and LVM in excess of that predicted from stroke work (inappropriate LVM, LVM_{inappr}) in all participants (LVMI: partial r=-0.18, p<0.0001; LVM_{inappr}: partial r=-0.17, p<0.0001) and NT (LVMI: partial r=-0.23, p<0.0001; LVM_{inappr}: partial r=-0.22, p<0.0001) separate from hypertensives. Marked differences in LVM_{inappr} were noted in the eGFR range <132 compared to ≥132 mls/min/1.73m^2 (p<0.0005). When replacing clinic BP with either aortic systolic BP, 24-hour BP, PWV, stroke work (for LVMI), LV end diastolic diameter (LVEDD), or circumferential wall stress in the regression models, eGFR retained strong associations with LVMI (p=0.01 to <0.0001) and LVM_{inappr} (p<0.005 to <0.0001) and these effects were replicated in NT separate from hypertensives. In conclusion, strong relationships between eGFR and LVM occur at a community level irrespective of the presence of hypertension and independent of 24-hour and aortic BP, PWV, LVEDD, stroke work and wall stress. Non-haemodynamic factors explain a considerable proportion of the relationship between early glomerular dysfunction and LV hypertrophy.

4.1 Introduction

Chronic kidney disease (CKD) preceding the development of renal failure, is independently associated with cardiovascular outcomes (Culleton et al 1999, Mann et al 2001, Sclipak et al 2002, Henry et al 2002, Manjunath et al 2003, Go et al 2004, Anavekar et al 2004, Farbom et al 2008, Vanholder et al 2005, Hallen et al 2007, McCullough et al 2007, Foster et al 2007, Cirillo et al 2008). A number of mechanisms may explain this relation including haemodynamic and non-haemodynamic factors (Culleton et al 1999, Fliser et al 1998, Kronenberg et al 2000, Stam et al 2003). An important finding lending insights into the relationship between early CKD and cardiovascular outcomes, is the strong relationship noted between renal impairment and left ventricular mass (LVM) well in advance of overt renal failure (Levin et al 1996, Landray et al 2001, Leoncini et al 2003, Leoncini et al 2004, Henry et al 2005, Paoletti et al 2005, Leoncini et al 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata et al 2010, Cioffi et al 2011). However, the contribution of haemodynamic versus non-haemodynamic factors to this relationship is uncertain.

Although associations between early CKD and LVM have consistently been demonstrated to be independent of conventional blood pressure (BP) (Levin et al 1996, Landray et al 2001, Leoncini et al 2003, Leoncini et al 2004, Henry et al 2005, Paoletti et al 2005, Leoncini et al 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata et al 2010, Cioffi et al 2011), these studies have largely been conducted in select clinical samples of which 66-100% of participants were either hypertensive or had a history of hypertension. Residual confounding long-term haemodynamic effects produced by hypertension may therefore explain these relations (Levin et al 1996, Landray et al 2001, Leoncini et al 2003, Leoncini et al 2004, Henry et al 2005, Paoletti et al 2005, Leoncini et al 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata et al 2010, Cioffi et al 2011). Moreover, arterial stiffness has been reported to account for associations between early CKD and LVM (Henry et al 2005), an effect that could be attributed to the

impact of increases in arterial stiffness on aortic BP. In this regard, aortic BP is associated with LVM beyond brachial BP (Norton et al 2012). Furthermore, with adjustments for 24-hour BP, only a trend ($p<0.05$) for a relationship between early CKD and LVM in hypertensives persisted (Cerasola et al 2010). In this regard, it is also well-recognised that 24-hour BP may be more closely associated with LVM than conventional BP (Mancia and Parati 2000). It is therefore possible that the relationships between early CKD and LVM may not be entirely explained by haemodynamic factors. To caste further light on this issue, I assessed associations between early glomerular dysfunction and LVM in a community rather than in a hypertensive sample, and the extent to which these relations are determined by haemodynamic factors.

4.2 Methods

4.2.1 Study participants

The study participants were recruited as described on pages 56 to 57 in section 2.2.1 of chapter 2 of the present thesis. Of the 678 participants enrolled in an echocardiographic substudy, 621 participants had serum creatinine concentrations and percentage glycated haemoglobin (HbA1c) measurements. Of these participants, carotid-femoral pulse wave velocity (PWV) was available in 554 participants and ambulatory BP recordings that met with pre-specified quality control criteria (longer than 20 hours and more than 10 and 5 readings for the computation of daytime and night-time means, respectively) available in 437 participants.

4.2.2 Clinical, demographic, and anthropometric measurements

Clinical and demographic data were obtained using a standardised questionnaire as described on pages 57 to 58 in section 2.2.2 of chapter 2 of the present thesis.

Anthropometric data was obtained also as described on pages 57 to 58, in section 2.2.2 of chapter 2 of the present thesis. Participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2.

4.2.3 Blood collection and analysis

Blood analysis was performed as described on pages 58 to 59 in section 2.2.3 of chapter 2 of the present thesis.

4.2.4 Conventional blood pressure

Conventional (brachial) blood pressure (BP) measurements were performed as described on pages 59 to 60 in section 2.2.4 of chapter 2 of the present thesis. In the 621 participants the frequency of identical consecutive conventional recordings was 0.32% for systolic BP and 0.64% for diastolic BP. No conventional BP values were recorded as an odd number. Of the conventional systolic and diastolic BP readings, 30.9% ended on a zero (expected =20%). Hypertension was defined as the presence of antihypertensive therapy or a mean BP≥140/90 mm Hg.

4.2.5 Ambulatory blood pressure

Twenty four hour ambulatory BP monitoring was performed on the same day as conventional BP measurements using oscillometric monitors (SpaceLabs, model 90207) as previously described (Woodiwiss et al 2009). Monitors were programmed to measure BP at 15-minute intervals from 06:00 to 22:00 and at 30-minute intervals from 22:00 to 06:00. The calibration was checked monthly against a mercury manometer. The cuff size was the same as that used for conventional BP measurements. Intra-individual means of the ambulatory measurements were weighted by the time-interval between successive

recordings. The mean±SD number of BP recordings for the 24-hour period was 60.5±11.8 (range=24-81).

4.2.6 Renal function.

Estimated glomerular filtration rate (eGFR) was determined using the abbreviated Modification of Diet in Renal Disease (MDRD) study group equation: 186.3 x (serum creatinine in mg/decilitre$^{-1.154}$) x (age in years$^{-0.203}$) x 1.212 x 0.742 (if female) (Levey et al 1999).

4.2.7 Pulse wave analysis.

Aortic BP and carotid-femoral PWV were determined using applanation tonometry and SphygmoCor software as previously described (Woodiwiss et al 2009, Norton et al 2012, Redelinghuys et al 2010). Pulse wave analysis was determined after participants had rested for 15 minutes in the supine position. Arterial waveforms at the radial (dominant arm), carotid and femoral artery pulses were recorded by applanation tonometry, each during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). To determine aortic BP, the pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. The radial pressure waveform was converted into a central (aortic) waveform using a validated generalised transfer function incorporated in SphymoCor software. Central aortic systolic and diastolic BP were derived from the aortic waveform. A typical example of the radial and aortic BP data obtained from pulse wave analysis is shown in Figure 4.1. Aortic augmentation index (AIx) was calculated as the difference between the second and the first systolic peak of the aortic waveform (augmentation pressure) given as a percentage of the aortic pulse pressure. The time

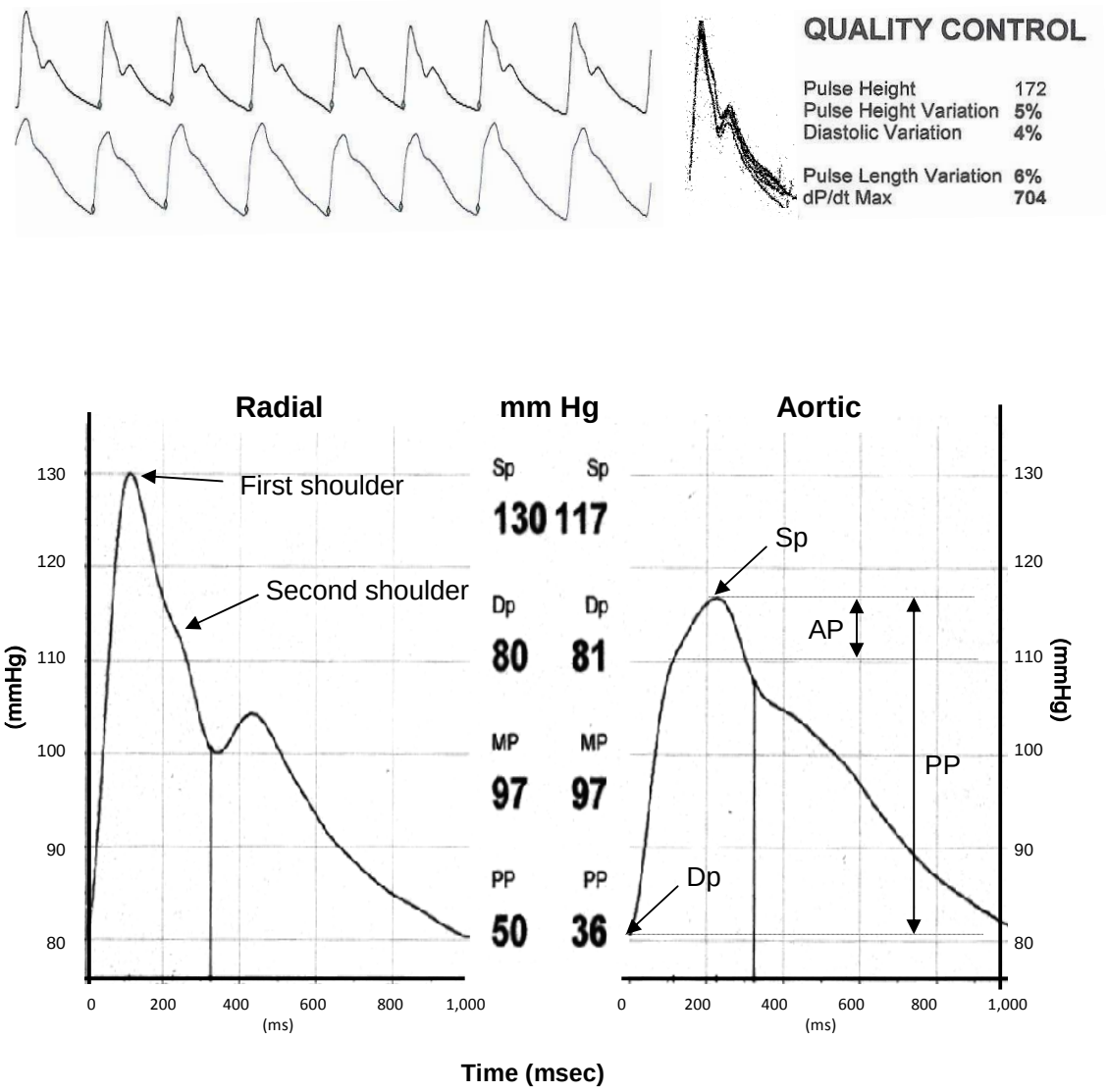

Figure 4.1. Example of a pulse wave recording obtained to determine central haemodynamics. The figure shows the radial artery pulse wave obtained from applanation tonometry (lower left panel) and the aortic pulse wave derived from a population-based transfer function built into the software (lower right panel). See text for a further description. Quality control assessments are shown in the top panel. Sp, systolic blood pressure (BP); Dp, diastolic BP; MP, mean arterial pressure; PP, pulse pressure; AP, augmentation pressure.

delay in the pulse waves between the carotid and femoral sites was determined using an electrocardiograph-derived R wave as a fiducial point. A typical example of the carotid and femoral artery traces obtained using applanation tonometry and the method used to determine the time delay for wave travel from the carotid to the femoral sites is shown in Figure 4.2. The distance from the suprasternal notch to the carotid sampling site (A) and from the suprasternal notch to the femoral artery (B) was measured. Pulse wave velocity distance was calculated as B minus A. Pulse transit time was taken as the average of 10 consecutive beats. Aortic PWV was calculated as the ratio of the distance to the transit time (m/sec).

4.2.8. Echocardiography

Echocardiographic measurements were performed using two-dimensional targeted M-mode echocardiography as described on pages 62 to 64 in section 2.2.6 of chapter 2 of the present thesis. Stroke volume was evaluated from the difference between LV end diastolic and systolic volumes determined using the Teichholz method (Teichholz et al 1976). Using this method left ventricular end systolic volume (LVESV) was calculated using the equation $LVESV = [7.0/ (2.4 + LVESD)] \times (LVESD)^3$ whilst left ventricular end diastolic volume (LVEDV) was calculated using the equation: $LVEDV = [7.0/(2.4 + LVEDD)] \times (LVEDD)^3$ (Teichholz et al 1976). Circumferential LV systolic wall stress was calculated as:

$$\frac{SBP\ (0.5\ LVIDs)^2\ [1+ \{(0.5\ LVIDs + PWTs)^2/(0.5\ LVIDs + 0.5\ PWTs)^2\}]}{(0.5\ LVIDs + PWTs)^2 - (0.5\ LVIDs)^2}$$

where SBP is systolic blood pressure, LVIDs is LVID in systole and PWTs is posterior wall thickness in systole (Shimizu et al 1991). As stroke work (systolic BP and stroke volume), height and gender are the major factors that determine most of the variability in LVM at a population level, it has been postulated that LVH that exceeds that which would be expected from these changes reflects an inappropriate LVH. The extent of inappropriate LVM (LVM_{inappr}) was therefore determined from predicted LVM as previously described (de

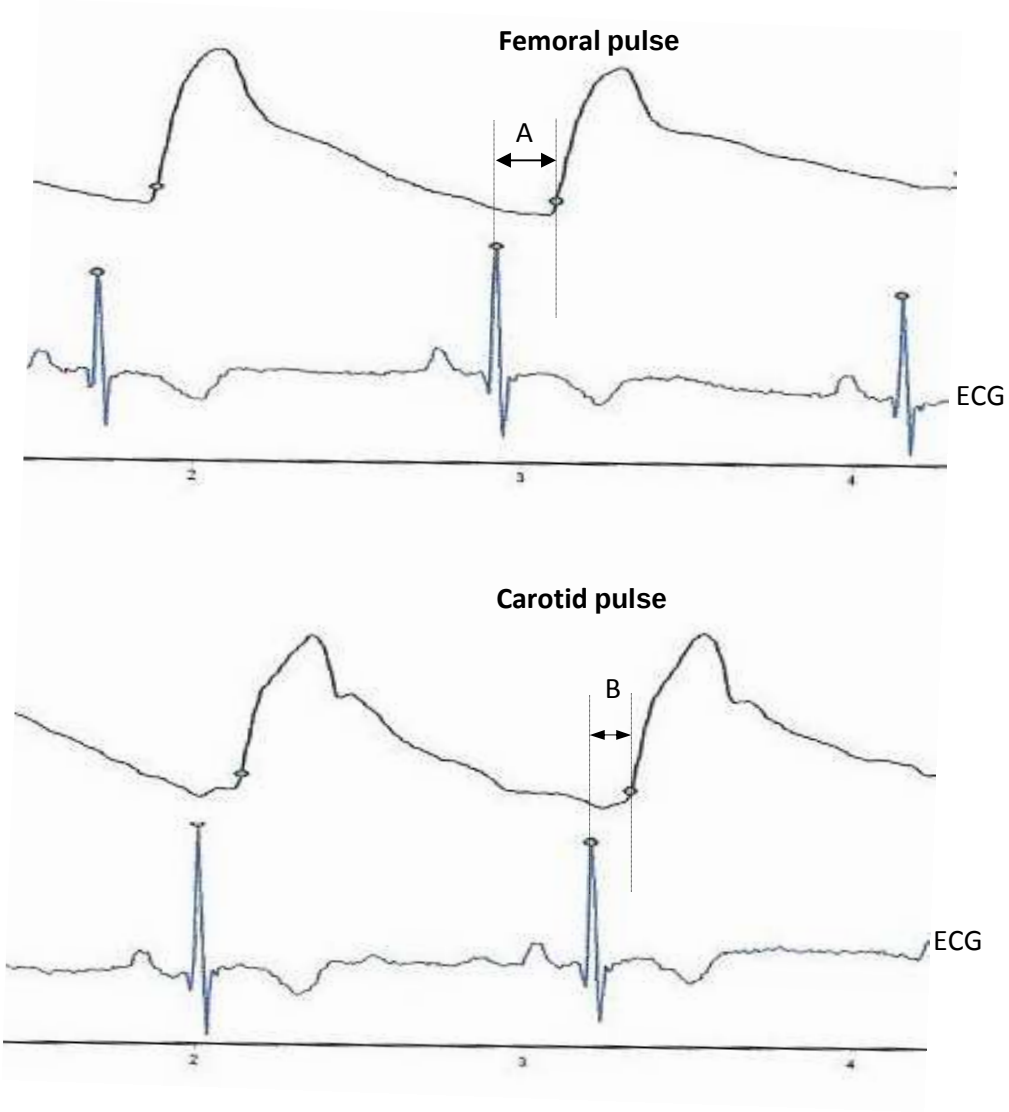

Figure 4.2 Examples of femoral and carotid artery pulse waves obtained using applanation tonometry from the same participants. Together with simultaneous electrocardiographic (ECG) recordings aortic pulse wave velocity (PWV) is calculated. The arrows indicate the time between electrical events and the arterial pressure changes in the carotid and femoral arteries used to calculate PWV. See text for a further description.

Simone et al 2002) where predicted LVM was calculated as 55.37+(6.64 x height$^{2.7}$)+(0.64 x [systolic BP x stroke volume x 0.014]) –(18.07 x gender), where male gender=1 and female gender=2, and where stroke volume was calculated from LV volumes assessed from the Teichholz method. Inappropriate LVM was expressed as % actual LVM/predicted LVM. An $LVMI_{inappr}$>150% was considered to be increased. This threshold was identified from the upper 95% confidence interval for $LVMI_{inappr}$ determined in 140 participants without clinically significant disease and normal blood parameters who were normotensive, non-diabetic, and had a BMI<30 kg/m^2. In these participants the upper 95% confidence for LVMI was 51.8 g/m$^{2.7}$.

4.2.9. Data analysis

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. Relationships were determined using multivariate regression analysis with adjustments for clinic BP (or alternative haemodynamic factors), age, sex, waist circumference, HbA1c, regular tobacco intake, regular alcohol intake, pulse rate and treatment for hypertension in the models. To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). To confirm that relationships between eGFR and LVMI or LVM_{inappr} observed in the whole group were not only because of the presence of hypertension, sensitivity analysis was conducted in normotensives and hypertensives separately. As diabetes mellitus or an abnormal blood glucose control may be associated with both an impaired renal function and LVH, sensitivity analysis was also conducted in non-diabetic participants and in those with an HbA1c<6.1% separate from those either receiving treatment for diabetes mellitus or whom had an HbA1c>6.1%. To compare relationships,

analyses were obtained from data sets of comparable sample sizes by imputing missing data for PWV and 24-hour BP using the Markov chain Monte Carlo method (for an arbitrary missing data pattern) of multiple imputation as implemented by the PROC MI and PROC MIANALYSE procedures incorporated in the SAS package. The mean of five imputations created for each of the missing values was employed for analysis. Regression relations were compared using Z statistics. Probability values <0.05 were considered to be significant.

4.3 Results

4.3.1 Participant characteristics.

The characteristics of the normotensives and the hypertensives are shown in Table 4.1. In general more women participated in the study and the study group had a high prevalence of obesity. In the treated hypertensives 85.5% of participants were receiving low dose hydrochlorothiazide, 15.9% calcium channel blockers, 20.7% angiotensin-converting enzyme inhibitors and 2.0% beta adrenergic receptor blockers (β-blockers). None of the participants had a history of cardiovascular disease. The characteristics of those with as compared to those without echocardiography, as well as both eGFR and HbA1c measurements are shown in Table 4.2. No differences were noted between the groups.

Table 4.1. Characteristics of participants.

	NT (n=332)	HT (n=289)	p value
Sex (% female)	66.0	63.7	NS
Age (years)	33.0±13.5	54.4±15.0	<0.0001
Body mass index (kg/m^2)	27.0±7.0	32.0±7.6	<0.0001
Waist circumference (cm)	84.1±14.7	97.2±15.8	<0.0001
% Overweight/obese	25.3/29.5	22.8/56.4	S/<0.0001
Regular tobacco intake (%)	14.8	13.8	NS
Regular alcohol intake (%)	20.2	20.4	NS
% DM of HbA1c>6.1%	11.5	45.0	<0.0001
% Treated for HT	0	50.2	<0.0001
Pulse rate (beats/min)	69±11	69±10	NS
Conventional SBP/DBP (mm Hg)	115±11/77±8	145±22/92±13	0.0001/<0.0001
Aortic SBP/DBP (mm Hg)	107±12/77±8	136±23/92±14	<0.0001/<0.0001
24 hour SBP (mm Hg) (n)	111±9 (232)	127±16 (205)	<0.0001
24 hour DBP (mm Hg) (n)	68±7 (232)	78±11 (205)	<0.0001
Aortic pulse wave velocity (m/sec) (n)	4.91±1.45 (303)	7.66±3.18 (251)	<0.0001
Aortic augmentation index (%)	22.9±13.4	31.7±10.5	<0.0001
Stroke work (g-m)	100±31	132±40	<0.0001
LV systolic wall stress (g/cm^2)	105±23	121±34	<0.0001
% Increased serum creatinine	1.5	8.3	<0.0001
eGFR (mls/min/1.73 m^2)	124±29	103±29	<0.0001
Left ventricular mass (LVM) (g)	143±44	170±54	<0.0001
LVM index (g/m$^{2.7}$)	38.8±11.6	47.5±15.7	<0.0001
Inappropriate LVM (LVM_{inappr}) (%)	126±29	128±34	NS
LV mean wall thickness (mm)	0.84±0.18	0.95±0.21	<0.0001
LV end diastolic diameter (mm)	4.70±0.54	4.81±0.59	<0.05
% LV hypertrophy	12.7	32.9	<0.0001
% increased LVM_{inappr}	15.1	22.2	<0.01

Data are shown as mean±SD or %. NT, normotension; HT, hypertension; NS, non-significant; DM, diabetes mellitus; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; eGFR, estimated glomerular filtration rate.

Table 4.2. Characteristics of participants with and without echocardiography and other data.

	With (n=621)	Without (n=570)
Sex (% female)	64.9	65.6
Age (years)	42.9±17.8	44.2±18.5
Body mass index (kg/m^2)	29.3±7.7	29.7±8.4
Waist circumference (cm)	90.2±16.5	90.3±16.8
% Overweight/obese	24.2/42.0	21.8/43.5
Regular tobacco intake (%)	14.3	15.6
Regular alcohol intake (%)	20.1	22.3
Conventional SBP/DBP (mm Hg)	129±23/84±13	130±23/84±13

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

4.3.2 Haemodynamic factors associated with LVM or indices of CKD.

In bivariate analysis conventional, aortic, and 24-hour systolic BP, stroke work, PWV, and AIx were all correlated with LVMI and eGFR ($p<0.0001$ for all). Circumferential wall stress was correlated with eGFR ($p<0.001$) and LVM_{inappr} ($p<0001$).

4.3.3 Relationships between CKD and LVM.

On bivariate (Figure 4.3) and multivariate analysis (Table 4.3), including conventional systolic BP as a confounder, eGFR was related to LVMI and LVM_{inappr}. These relationships were reproduced in normotensives and in hypertensives (Table 4.3) and in non-diabetics and those with an HbA1c<6.1% (Table 4.4) separate from those with diabetes mellitus and/or those with an HbA1c>6.1%. In a multivariate regression model with eGFR, age, sex, conventional systolic BP, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, treatment for hypertension and HbA1c included in the model, conventional systolic BP (standardized β-coefficient=0.152±0.043, confidence intervals=0.07 to 0.24, p=0.0005), waist circumference (standardized β-coefficient=0.224±0.043, confidence intervals=0.14 to 0.31, p<0.0001) and eGFR (standardized β-coefficient=-0.176±0.040, confidence intervals=-0.25 to -0.10, p<0.0001) were the three main factors associated with LVMI. The magnitude of the effect of eGFR on LVMI was equivalent to that of waist circumference (p=0.41 for comparison of standardized β-coefficients). Similarly, in a multivariate regression model with all associated factors included in the model, waist circumference (standardized β-coefficient=0.298±0.044, confidence intervals=0.21 to 0.38, p<0.0001) and eGFR (standardized β-coefficient=-0.179±0.041, confidence intervals=-0.26 to -0.10, p<0.0001) were the two main factors associated with LVM_{inappr}.

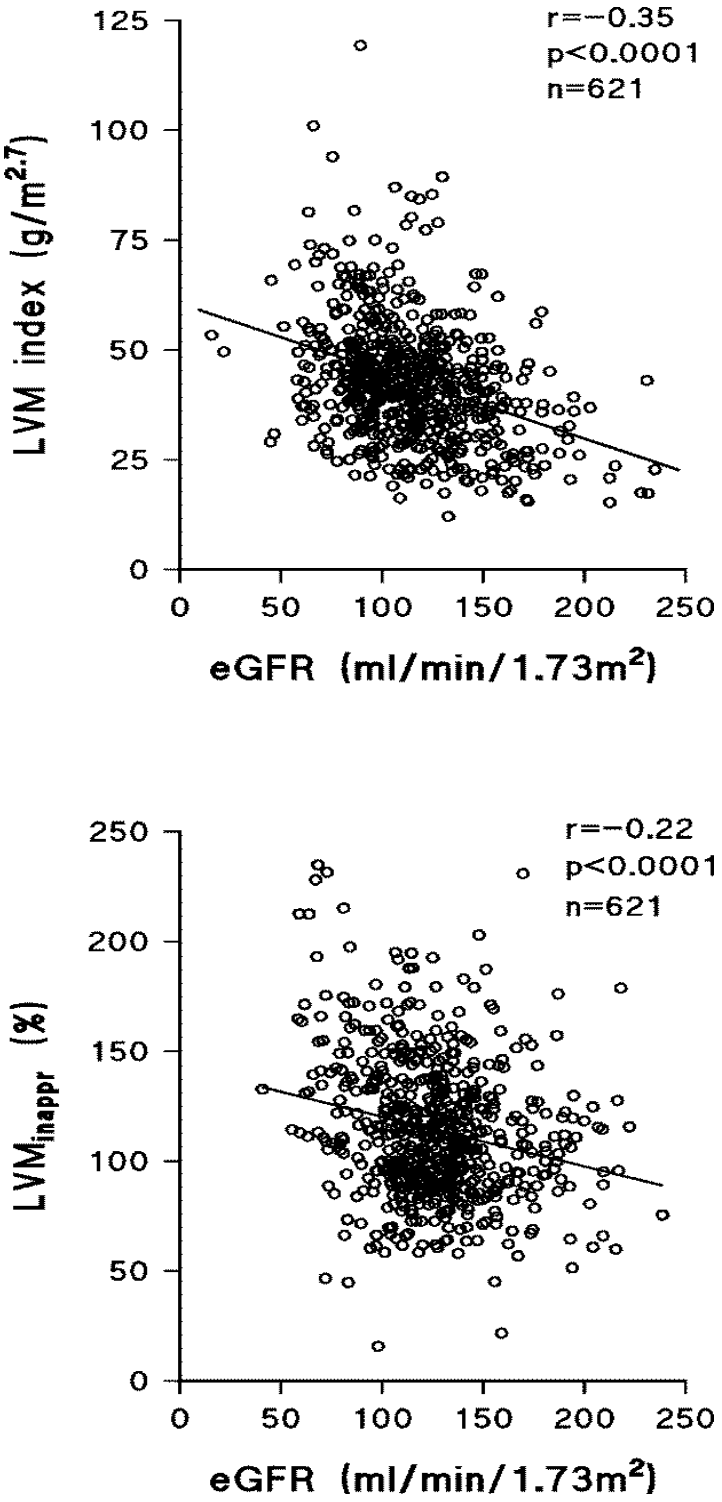

Figure 4.3. Bivariate relationships between estimated glomerular filtration rate (eGFR) and left ventricular mass (LVM) index (upper panel) or inappropriate LVM (LVM_{inappr}) (lower panel) in a community sample. See Table 4.3 for multivariate adjusted relationships.

Table 4.3. Multivariate adjusted (Partial r) relationships (correlation coefficients [95% confidence intervals]) and the slopes (β-coefficients) of the relationships between estimated glomerular filtration rate (eGFR) and left ventricular mass (LVM) index or inappropriate LVM (LVM_{inappr}) in a community sample.

eGFR versus	Partial r*	CI	p value†	β-coeff.±SEM	p value†
		<u>All participants</u> (n=621)			
Left ventricular mass index	-0.18	-0.25 to -0.10	<0.0001	-0.077±0.018	<0.0001
LVM_{inappr}	-0.17	-0.25 to -0.09	<0.0001	-0.170±0.039	<0.0001
		<u>Normotensives</u> (n=332)			
Left ventricular mass index	-0.23	-0.33 to -0.13	<0.0001	-0.100±0.020	<0.0001
LVM_{inappr}	-0.22	-0.33 to -0.12	<0.0001	-0.205±0.050	<0.0001
		<u>Hypertensives</u> (n=289)			
Left ventricular mass index	-0.12	-0.24 to -0.01	<0.05	-0.070±0.033	<0.05
LVM_{inappr}	-0.14	-0.25 to -0.02	<0.05	-0.161±0.070	<0.05

*Adjustments are for age, sex, clinic systolic blood pressure, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, HbA1c, and treatment for hypertension (in all participants). †Probability values were further adjusted for non-independence of family members. No differences in the partial r values (Z statistics) or β-coefficients were noted between normotensives and hypertensives.

Table 4.4. Unadjusted (Pearson's r) and multivariate adjusted (Partial r) relationships (correlation coefficients [95% confidence intervals]) and slopes (β-coefficients) of the relationships between estimated glomerular filtration rate (eGFR) and left ventricular mass (LVM) index or inappropriate LVM (LVM_{inappr}) in non-diabetics and those with an HbA1c<6.1% from a community sample (n=444).

eGFR versus	Pearson's r	CI	p value	Partial r*	CI	p value†	β-coeff.±SEM	p value†
Left ventricular mass index	-0.35	-0.43 to -0.27	<0.0001	-0.21	-0.30 to -0.12	<0.0001	-0.082±0.019	<0.0001
LVM_{inappr}	-0.22	-0.30 to -0.13	<0.0001	-0.23	-0.32 to -0.14	<0.0001	-0.204±0.042	<0.0001

*Adjustments are for age, sex, clinic systolic blood pressure, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, and treatment for hypertension. †Probability values were further adjusted for non-independence of family members.

4.3.4 LVM across quartiles of estimated glomerular filtration rate.

With adjustments for confounders including clinic systolic BP; LVMI and LVM_{inappr} increased with decreasing quartiles of eGFR (Table 4.5). These differences were replicated in normotensives and hypertensives separately and in non-diabetics and those with an HbA1c<6.1% separate from those with diabetes mellitus and/or those with an HbA1c>6.1% (Tables 4.6-4.8). The differences in multivariate adjusted LVMI and LVM_{inappr} were noticeable from the second as compared to the first quartile of eGFR and well before eGFR values that are consistent with stage 2 CKD (Table 4.5).

4.3.5 Impact of adjustments for haemodynamic factors on the relationships between estimated glomerular filtration rate and LVM.

The strength of the multivariate adjusted relationships between indices of CKD and LVM or LVM_{inappr} remained unchanged with adjustments for aortic BP, 24-hour BP, aortic PWV, stroke work (for LVMI), LV end diastolic diameter, or circumferential wall stress (Table 4.9). The haemodynamic-independent relationships between eGFR and LVMI or LVM_{inappr} were replicated in normotensives and hypertensives separately and in non-diabetics and those with an HbA1c<6.1% separate from those with diabetes mellitus and/or those with an HbA1c>6.1% (Tables 4.10-4.12).

Table 4.5. Unadjusted and multivariate adjusted left ventricular mass index (LVMI) or inappropriate LVM (LVM_{inappr}) at decreasing quartiles of estimated glomerular filtration rate (eGFR) in a community sample (n=621).

Quartiles (n)	1 (n=156)	2 (n=155)	3 (n=155)	4 (n=155)	p-values (versus quartile 1)†		
eGFR range (mls/min/1.73 m^2)	≥132	<132 and ≥111	<111 and ≥92	<92	2 vs 1	3 vs 1	4 vs 1
eGFR (mls/min/1.73 m^2)	156±21	120±6	100±5	78±13	<0.0001	<0.0001	<0.0001
Unadjusted LVMI ($g/m^{2.7}$)	35.6±11.5	42.3±13.7	44.3±12.1	48.9±16.0	<0.0001	<0.0001	<0.0001
Multivariate adjusted* LVMI ($g/m^{2.7}$)	38.7±13.3	43.3±12.7	43.7±12.5	45.4±13.8	=0.001	<0.0005	<0.0001
Unadjusted LVM_{inappr} (%)	114±31	128±30	130±27	133±30	<0.0001	<0.0001	<0.0001
Multivariate adjusted* LVM_{inappr} (%)	117±29	128±28	128±28	132±30	<0.0005	<0.001	<0.0001

*Adjustments are for age, sex, clinic systolic blood pressure, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, HbA1c, and treatment for hypertension. †Probability values were further adjusted for non-independence of family members.

Table 4.6. Unadjusted and multivariate adjusted left ventricular mass index (LVMI) or inappropriate LVM (LVM_{inappr}) at decreasing quartiles of estimated glomerular filtration rate (eGFR) in normotensives from a community sample (n=332).

Quartiles (n)	1 (n=82)	2 (n=83)	3 (n=83)	4 (n=84)	p-values (versus quartile 1)†		
eGFR range (mls/min/1.73 m^2)	≥143	<143 and ≥118	<118 and ≥100	<100	2 vs 1	3 vs 1	4 vs 1
eGFR (mls/min/1.73 m^2)	167±21	129±7	110±5	89±9	<0.0001	<0.0001	<0.0001
Unadjusted LVMI ($g/m^{2.7}$)	33.3±10.5	38.3±11.3	40.3±10.5	43.4±11.9	<0.005	<0.0001	<0.0001
Multivariate adjusted* LVMI ($g/m^{2.7}$)	34.8±10.9	39.6±10.7	40.2±10.6	41.5±11.4	<0.005	=0.001	<0.0001
Unadjusted LVM_{inappr} (%)	115±30	123±26	129±28	133±24	<0.05	=0.001	<0.0001
Multivariate adjusted* LVM_{inappr} (%)	117±26	127±27	127±26	129±28	<0.05	=0.01	<0.01

*Adjustments are for age, sex, clinic systolic blood pressure, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, and HbA1c. †Probability values were further adjusted for non-independence of family members.

Table 4.7. Unadjusted and multivariate adjusted left ventricular mass index (LVMI) or inappropriate LVM (LVM_{inappr}) at decreasing quartiles of estimated glomerular filtration rate (eGFR) in hypertensives from a community sample (n=289).

Quartiles (n)	1 (n=72)	2 (n=71)	3 (n=75)	4 (n=71)	p-values (versus quartile 1)†		
eGFR range (mls/min/1.73 m^2)	≥122	<122 and ≥100	<100 and ≥86	<86	2 vs 1	3 vs 1	4 vs 1
eGFR (mls/min/1.73 m^2)	141±18	110±6	92±4	69±14	<0.0001	<0.0001	<0.0001
Unadjusted LVMI ($g/m^{2.7}$)	41.2±15.0	47.2±14.9	47.5±14.6	52.2±17.2	=0.01	<0.01	<0.0001
Multivariate adjusted* LVMI ($g/m^{2.7}$)	41.9±14.2	48.0±14.4	48.1±14.6	50.0±15.4	<0.05	<0.05	<0.005
Unadjusted LVM_{inappr} (%)	116±35	129±36	130±29	134±35	<0.05	<0.01	<0.005
Multivariate adjusted* LVM_{inappr} (%)	117±30	128±31	131±31	133±33	<0.05	<0.01	<0.01

*Adjustments are for age, sex, clinic systolic blood pressure, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, HbA1c and treatment for hypertension. †Probability values were further adjusted for non-independence of family members.

Table 4.8. Unadjusted and multivariate adjusted left ventricular mass index (LVMI) or inappropriate LVM (LVM_{inappr}) at decreasing quartiles of estimated glomerular filtration rate (eGFR) in non-diabetics and those with an HbA1c<6.1% from a community sample (n=444).

Quartiles (n)	1 (n=111)	2 (n=111)	3 (n=111)	4 (n=111)	p-values (versus quartile 1)†		
eGFR range (mls/min/1.73 m^2)	≥136	<136 and ≥113	<113 and ≥95	<95	2 vs 1	3 vs 1	4 vs 1
eGFR (mls/min/1.73 m^2)	163±25	123±7	104±6	83±11	<0.0001	<0.0001	<0.0001
Unadjusted LVMI ($g/m^{2.7}$)	34.2±11.2	40.3±11.5	41.6±11.1	46.2±13.7	=0.0001	<0.0001	<0.0001
Multivariate adjusted* LVMI ($g/m^{2.7}$)	36.6±11.8	40.6±11.5	40.7±11.4	43.5±12.5	<0.005	<0.005	<0.0001
Unadjusted LVM_{inappr} (%)	113±31	124±28	126±28	128±26	<0.005	=0.0005	<0.0001
Multivariate adjusted* LVM_{inappr} (%)	113±26	124±26	124±25	128±28	<0.005	<0.005	=0.0001

*Adjustments are for age, sex, clinic systolic blood pressure, waist circumference, pulse rate, regular tobacco use, regular alcohol intake and treatment for hypertension. †Probability values were further adjusted for non-independence of family members.

Table 4.9. Impact of adjustments for haemodynamic factors on the multivariate adjusted (partial r) relationships (correlation coefficients [95% confidence intervals]) between estimated glomerular filtration rate (eGFR) and left ventricular mass index (LVMI) and inappropriate LVM (LVM_{inappr}) in a community sample (n=621).

eGFR versus	Adjustments	Partial r*	CI	p value†
LVMI	*+ SBPclinic	-0.18	-0.25 to -0.10	<0.0001
	*+ SBPaortic	-0.16	-0.24 to -0.09	<0.0001
	*+ PWV	-0.17	-0.25 to -0.09	<0.0001
	*+ SBP24 hr	-0.18	-0.25 to -0.10	<0.0001
	*+ LVEDD	-0.21	-0.29 to -0.13	<0.0001
	*+ Stroke work	-0.10	-0.18 to -0.02	=0.01
	*+ Systolic stress	-0.17	-0.24 to -0.09	<0.0001
LVM_{inappr}	*+ SBPclinic	-0.17	-0.25 to -0.09	<0.0001
	*+ SBPaortic	-0.17	-0.24 to -0.09	<0.0001
	*+ PWV	-0.16	-0.24 to -0.09	<0.0001
	*+ SBP24 hr	-0.17	-0.24 to -0.09	<0.0001
	*+ LVEDD	-0.16	-0.23 to -0.08	=0.0001
	*+ Systolic stress	-0.12	-0.19 to -0.04	<0.005

CI, confidence intervals; SBP, systolic blood pressure; PWV, aortic pulse wave velocity; 24 hr, 24-hour; LVEDD, left ventricular end diastolic diameter. *Adjustments are for age, sex, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, HbA1c, and treatment for hypertension. †Probability values were further adjusted for non-independence of family members. Missing values for PWV and 24-hour were imputed as described in the data analysis. No differences in relationships were noted (Z statistics).

Table 4.10. Impact of adjustments for haemodynamic factors on the multivariate adjusted (partial r) relationships (correlation coefficients [95% confidence intervals]) between estimated glomerular filtration rate (eGFR) and left ventricular mass index (LVMI) and inappropriate LVM (LVM_{inappr}) in normotensives from a community sample (n=332).

eGFR versus	Adjustments	Partial r*	CI	p value†
LVMI	*+ SBPclinic	-0.23	-0.33 to -0.13	<0.0001
	*+ SBPaortic	-0.21	-0.31 to -0.10	=0.0001
	*+ PWV	-0.25	-0.35 to -0.14	<0.0001
	*+ SBP24 hr	-0.29	-0.38 to -0.18	<0.0001
	*+ LVEDD	-0.26	-0.36 to -0.15	<0.0001
	*+ Stroke work	-0.11	-0.22 to -0.01	<0.05
	*+ Systolic stress	-0.24	-0.34 to -0.14	<0.0001
LVM_{inappr}	*+ SBPclinic	-0.22	-0.33 to -0.13	<0.0001
	*+ SBPaortic	-0.21	-0.31 to -0.10	<0.0005
	*+ PWV	-0.21	-0.31 to -0.10	<0.0005
	*+ SBP24 hr	-0.21	-0.31 to -0.10	<0.0005
	*+ LVEDD	-0.17	-0.27 to -0.06	<0.005
	*+ Systolic stress	-0.18	-0.28 to -0.07	<0.005

CI, confidence intervals; SBP, systolic blood pressure; PWV, aortic pulse wave velocity; 24 hr, 24-hour; LVEDD, left ventricular end diastolic diameter. *Adjustments are for age, sex, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, and HbA1c. †Probability values were further adjusted for non-independence of family members. Missing values for PWV and 24-hour were imputed as described in the data analysis. No differences in relationships were noted (Z statistics).

Table 4.11. Impact of adjustments for haemodynamic factors on the multivariate adjusted (partial r) relationships (correlation coefficients [95% confidence intervals]) between estimated glomerular filtration rate (eGFR) and left ventricular mass index (LVMI) and inappropriate LVM (LVM_{inappr}) in hypertensives from a community sample (n=289).

eGFR versus	Adjustments	Partial r*	CI	p value†
LVMI	*+ SBPclinic	-0.12	-0.24 to -0.004	<0.05
	*+ SBPaortic	-0.12	-0.23 to -0.001	<0.05
	*+ PWV	-0.12	-0.24 to -0.004	<0.05
	*+ SBP24 hr	-0.12	-0.24 to -0.005	<0.05
	*+ LVEDD	-0.20	-0.31 to -0.09	<0.001
	*+ Stroke work	-0.11	-0.22 to 0.008	=0.07
	*+ Systolic stress	-0.11	-0.23 to 0.006	=0.06
LVM_{inappr}	*+ SBPclinic	-0.17	-0.28 to -0.05	<0.005
	*+ SBPaortic	-0.16	-0.27 to -0.04	<0.01
	*+ PWV	-0.18	-0.29 to -0.07	<0.005
	*+ SBP24 hr	-0.17	-0.29 to -0.06	<0.005
	*+ LVEDD	-0.18	-0.29 to -0.06	<0.005
	*+ Systolic stress	-0.12	-0.23 to -0.001	<0.05

CI, confidence intervals; SBP, systolic blood pressure; PWV, aortic pulse wave velocity; 24 hr, 24-hour; LVEDD, left ventricular end diastolic diameter. *Adjustments are for age, sex, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, HbA1c and treatment for hypertension. †Probability values were further adjusted for non-independence of family members. Missing values for PWV and 24-hour were imputed as described in the data analysis. No differences in relationships were noted (Z statistics).

Table 4.12. Impact of adjustments for haemodynamic factors on the multivariate adjusted (partial r) relationships (correlation coefficients [95% confidence intervals]) between estimated glomerular filtration rate (eGFR) and left ventricular mass index (LVMI) and inappropriate LVM (LVM_{inappr}) in non-diabetics and those with an HbA1c<6.1% from a community sample (n=444).

eGFR versus	Adjustments	Partial r*	CI	p value†
LVMI	*+ SBPclinic	-0.21	-0.30 to -0.12	<0.0001
	*+ SBPaortic	-0.20	-0.29 to -0.11	<0.0001
	*+ PWV	-0.18	-0.27 to -0.08	<0.0005
	*+ SBP24 hr	-0.21	-0.30 to -0.12	<0.0001
	*+ LVEDD	-0.25	-0.34 to -0.16	<0.0001
	*+ stroke work	-0.13	-0.22 to -0.03	<0.01
	*+ Systolic stress	-0.20	-0.29 to -0.11	<0.0001
LVM_{inappr}	*+ SBPclinic	-0.21	-0.30 to -0.12	<0.0001
	*+ SBPaortic	-0.20	-0.29 to -0.11	<0.0001
	*+ PWV	-0.20	-0.29 to -0.11	<0.0001
	*+ SBP24 hr	-0.20	-0.29 to -0.11	<0.0001
	*+ LVEDD	-0.19	-0.28 to -0.10	<0.0001
	*+ Systolic stress	-0.14	-0.23 to -0.05	<0.005

CI, confidence intervals; SBP, systolic blood pressure; PWV, aortic pulse wave velocity; 24 hr, 24-hour; LVEDD, left ventricular end diastolic diameter. *Adjustments are for age, sex, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, and treatment for hypertension. †Probability values were further adjusted for non-independence of family members. Missing values for PWV and 24-hour were imputed as described in the data analysis. No differences in relationships were noted (Z statistics).

4.4 Discussion

The main findings of the present study are as follows: In a randomly selected community sample of African ancestry, eGFR was independently related to LVMI and LVM_{inappr} and these associations were replicated in normotensives and hypertensives separately. The impact of eGFR on LVMI or LVM_{inappr} was noted well before early CKD. Furthermore, relationships between eGFR and LVMI or LVM_{inappr} were not influenced by adjustments for aortic BP, 24-hour BP, aortic PWV, stroke work, LV end diastolic diameter, or circumferential wall stress.

Although a number of studies have reported on relationships between indices of early CKD and LVMI or LVM_{inappr}, these studies were conducted in select clinical samples with a high prevalence of hypertension or history of hypertension (Levin et al 1996, Landray et al 2001, Leoncini et al 2003, Leoncini et al 2004, Henry et al 2005, Paoletti et al 2005, Leoncini et al 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata et al 2010, Cioffi et al 2011). Thus, these relationships (Levin et al 1996, Landray et al 2001, Leoncini et al 2003, Leoncini et al 2004, Henry et al 2005, Paoletti et al 2005, Leoncini et al 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata et al 2010, Cioffi et al 2011) may reflect a selection bias where residual confounding effects of long-term hypertensive target organ changes cannot be excluded. In contrast, to the best of our knowledge the present study is the first to show relationships between an index of CKD (eGFR) and LVMI or LVM_{inappr} in a randomly selected community sample, where these relationships cannot be attributed to the long-term effects of hypertension. Indeed, in sensitivity analysis conducted in normotensives only, strong independent relationships between eGFR and LVMI or LVM_{inappr} were noted. The results of the present study therefore support the notion that strong associations between early CKD and LVM may be attributed to factors other than hypertension.

The results of the present study suggest that haemodynamic effects are unlikely to explain associations between an early decrease in glomerular function and LVM. In

contrast to a previous study (Henry et al 2005) where relations between indices of early CKD and LVM were abolished with adjustments for indices of aortic stiffness, in the present study adjustments for neither carotid-femoral PWV nor aortic systolic BP modified the strong independent relations noted between eGFR and LVM. A possible explanation for this apparent discrepancy is that in the present study the mean (±SD) age of the study sample was 42.9±17.8 years, whilst in the previous study (Henry et al 2005) the mean (±SD) age of participants was 68.2±7.3 years for men and 69.1±6.7 years for women. In this regard, age is the strongest predictor of aortic stiffness. Moreover, with adjustments for 24-hour BP, only a trend ($p<0.05$) for a relationship between early CKD and LVM in hypertensives has previously been shown to persist (Cerasola et al 2010). However, in the present study I show a marked independent relationship between eGFR and LVM_{inappr} after adjusting for 24-hour BP ($p<0.0001$). The strong relationship noted between eGFR and LVM beyond that predicted from stroke work (LVM_{inappr}) in the present study conducted in a community sample is consistent with previous studies (Nardi et al 2009, Cioffi et al 2011) demonstrating similar effects in hypertensives only. The ability to reproduce these findings in normotensives separate from hypertensives, extends these studies (Nardi et al 2009, Cioffi et al 2011) by indicating that residual confounding effects of hypertensive-related increases in stroke work on LVM cannot explain these relations. Importantly, not previously reported on is the persistence of relations between eGFR and LVM after adjustments for LV end diastolic diameter and circumferential systolic wall stress in the present study, factors which could also increase in CKD through volume retention and LV dilatation.

The clinical implications of the present study warrant consideration. In view of the independent relationship that exists between LVM and cardiovascular outcomes, including the development of heart failure (Casale et al 1986, Levy et al 1990, Ghali et al 1992, Levy et al 1996, Gottdiener et al 2000, Gardin et al 2001), the present study provides support for the hypothesis that the development of LV hypertrophy (LVH) may, in-part explain the ability of early CKD to predict outcomes (Culleton et al 1999, Mann et al 2001,

Sclipak et al 2002, Henry et al 2002, Manjunath et al 2003, Go et al 2004, Anavekar et al 2004, Farbom et al 2008, Vanholder et al 2005, Hallen et al 2007, McCullough et al 2007, Foster et al 2007, Cirillo et al 2008). In this regard, the present study also suggests that decreases in eGFR that are considered to reflect changes in renal function well in advance of even stage 2 CKD, are associated with LVM beyond the presence of hypertension and alternative haemodynamic factors and hence that the use of BP lowering or diuretic therapy may not address the factors responsible for this relationship. As insulin resistance and increases in inflammatory markers are already present in patients with an impaired renal function (Fliser et al 1998, Stam et al 2003) and these changes may contribute toward LVH, it is possible that in those with early CKD, targeting these changes may be important for LVH regression and risk reduction. Further studies are required to address these hypotheses.

An important question which arises from the present study is given the independent relationship noted between eGFR and LVMI in the present study, could the assessment of eGFR enhance the ability to detect LVH in populations where ECG criteria have a poor specificity and performance?. In this regard, as indicated in chapter 3 of the present thesis, current ECG criteria for LVH detection yield either a negligible performance or too low a specificity in obese people of African ancestry to recommend their use. Further studies are required to address this question.

The limitations of the present study are as follows. The present study was a cross-sectional design and hence conclusions regarding cause and effect cannot be drawn. Whether early glomerular dysfunction is causally related to an increased LVM requires prospective evaluation. Second, a high proportion of participants were women and I was not statistically powered to perform sex-specific analyses. Third, I assessed the impact of haemodynamic factors on relations between eGFR and LVM in one ethnic group only. Hence, further studies are required to assess the consistency of the present findings in alternative ethnic groups.

In conclusion, the results of the present study indicate that in randomly selected participants from a community of African ancestry, a strong independent relationship exists between eGFR and LVM, well before the onset of renal failure and irrespective of whether participants had hypertension or not. This relationship was noted to be independent of aortic BP, 24-hour BP, aortic PWV, stroke work, LV end diastolic diameter, or circumferential wall stress and hence is likely to reflect the impact of non-haemodynamic factors. Prospective studies and intervention studies with BP lowering therapy and/or diuretic agents are required to determine whether early glomerular dysfunction predicts the development of LVH; the extent to which modifications in haemodynamic factors affect this relationship; and the non-haemodynamic factors that may explain this relationship. Moerover, whether the use of eGFR assessments may enhance the ability to detect LVH in populations where ECG criteria have a poor specificity and performance requires further study. In this regard, the latter question was addressed in chapter 6 of the present thesis.

CHAPTER 5

Relationship Between C-Reactive Protein and Left Ventricular Mass Independent of Co-Morbidities in a Community Sample with a High Prevalence of Risk-Related CRP.

Abstract

Whether the relationship between circulating C-reactive protein (CRP) concentrations and left ventricular mass (LVM) is independent of co-morbidities, is uncertain. In 361 randomly selected participants from a community with a high prevalence of CRP concentrations considered to be high-risk (54.0%), but without cardiovascular or renal disease, I evaluated the relationship between CRP and echocardiographically-determined LVM indexed to height$^{2.7}$ (LVMI) and inappropriate LVM (LVM_{inappr}). LVM_{inappr} was determined from the % of actual/predicted LVM. Serum CRP concentrations were correlated with both LVMI and LVM_{inappr} ($p<0.0001$). With adjustments for a number of potential confounders including age, systolic blood pressure, waist circumference (or body mass index), and glucose control (glycated haemoglobin), the relationships between serum CRP concentrations and both LVMI and LVM_{inappr} (partial $r=0.11$, $p<0.05$ for both) persisted. The independent relationship between CRP and LVMI or LVM_{inappr} translated into a markedly higher multivariate-adjusted LVMI and LVM_{inappr} values in the highest as compared to the lowest quartile of CRP (LVMI; highest quartile CRP=48.8±10.7, lowest quartile CRP=45.0±11.0, $p<0.05$; LVM_{inappr}; highest quartile CRP=137±28, lowest quartile CRP=127±24, $p<0.02$). In conclusion, CRP is associated with LVM independent of co-morbidities.

5.1 Introduction

Left ventricular hypertrophy (LVH) is well recognised as being an independent predictor of cardiovascular outcomes (Casale et al 1986, Levy et al 1990a, Koren et al 1991, Levy et al 1994, Verdercchia et al 1996, Ghali et al 1998, Devereux et al 2004, Okin et al 2004). Although these relationships are attributed in-part to the temporal accrual of the adverse effects of conventional risk factors on target organs, conventional risk factors may not be the only factors that explain LVH. In this regard, the role of chronic systemic inflammation, as indexed by circulating C-reactive protein (CRP) concentrations, as a possible determinant of LVH is uncertain.

C-reactive protein concentrations have been associated with LV mass (LVM) or LVH in the general population (Mehta et al 2007, Arnett et al 2011), in type II diabetes mellitus (Palmieri et al 2003), in hypertensives (Pedrinelli et al 2004, Conen et al 2006, Iwashima et al 2007, Assadi et al 2007, Ratto et al 2007, Assadi et al 2008, Masugata et al 2011, Torun et al 2012), in resistant hypertensives (Salles et al 2007), in patients hospitalised for myocardial infarction (Fertin et al 2010), in end-stage renal disease (Kim et al 2005, Monfared et al 2013), and in systemic lupus nephritis (Shi et al 2010). However, relationships reported on in these select clinical samples (Pedrinelli et al 2004, Conen et al 2006, Iwashima et al 2007, Assadi et al 2007, Ratto et al 2007, Assadi et al 2008, Masugata et al 2011, Torun et al 2012, Salles et al 2007, Fertin et al 2010, Kim et al 2005, Shi et al 2010, Monfared et al 2013) may represent the effects of a selection bias. Moreover, the relationships reported on in population studies (Mehta et al 2007, Palmieri et al 2003, Arnett et al 2011) may be attributed to the confounding effects of co-morbidities, including obesity, diabetes mellitus, or hypertension. Indeed, the direct relationships between CRP concentrations and LVH noted in two large population samples (n=2633-4973) were not independent of co-morbidities (Mehta et al 2007, Arnett et al 2011). Furthermore, the relationship between CRP and LVH in an alternative large (n=1299) population sample was only noted in those with type II diabetes mellitus

(Palmieri et al 2003). To caste further light on the possible independent association between CRP and LVM, in the present study I evaluated these relationships in a community sample with a high prevalence of risk-related circulating CRP concentrations (Redelinghuys et al 2011).

5.2 Methods

5.2.1 Study participants

The study participants were recruited as described on pages 56 to 57, in section 2.2.1 of chapter 2 of the present thesis. Of the 678 participants enrolled in an echocardiographic substudy, 361 participants had measures of blood high sensitivity CRP (hs-CRP) concentrations and percentage glycated haemoglobin (HbA1c).

5.2.2 Clinical, demographic, and anthropometric measurements

Clinical and demographic data were obtained using a standardised questionnaire as described on pages 57 to 58 in section 2.2.2 of chapter 2 of the present thesis. Anthropometric data was obtained also as described on pages 57 to 58, in section 2.2.2 of chapter 2 of the present thesis. Participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2.

5.2.3 Blood collection and analysis

Blood analysis was performed as described on pages 58 to 59 in section 2.2.3 of chapter 2 of the present thesis. Ultrasensitive-CRP (hs-CRP) concentrations (range 0.05-170 mg/l) was measured using an immunoturbidimetric assay performed on Olympus OSR 6185 reagent (Olympus Diagnostics, Lismeehan, Ireland) (inter- and intra-assay

coefficients of variation of 1.3% and 0.4%, respectively) and analysed using the Olympus AU640e Chemistry Immunoanalyser (Olympus, United Kingdom). Briefly the serum sample obtained from each participant was mixed with a 0.05% suspension of latex particles coated with goat antihuman CRP antibodies, in the presence of a biological buffer. The presence of CRP in the serum sample caused the antibodies to aggregate, resulting in a light scattering proportional to the CRP concentration in the serum. The presence of the aggregate was detected by reading the absorbance at 800nm. An hs-CRP concentration <1 mg/l was considered to be related to a low cardiovascular risk, 1-3 mg/l to moderate cardiovascular risk, and a concentration >3 mg/l to high cardiovascular risk (Pearson et al 2003).

5.2.4 Conventional blood pressure

Conventional (brachial) blood pressure (BP) measurements were performed as described on pages 59 to 60 in section 2.2.4 of chapter 2 of the present thesis. In the 361 participants the frequency of identical consecutive conventional recordings was 0.6% for systolic BP and 1.1% for diastolic BP. No conventional BP values were recorded as an odd number. Of the conventional systolic and diastolic BP readings, 28.4% ended on a zero (expected =20%). Hypertension was defined as the presence of antihypertensive therapy or a mean BP≥140/90 mm Hg.

5.2.5. Echocardiography

Echocardiographic measurements were performed using two-dimensional targeted M-mode echocardiography as described on pages 62 to 64 in section 2.2.6 of chapter 2 of the present thesis. The extent of inappropriate LVM (LVM_{inappr}) was determined as described on pages 97 to 99 in section 4.2.8 of chapter 4 of the present thesis.

5.2.6. Data analysis

For database management and statistical analysis, SAS software, version 9.1 (SAS Institute Inc., Cary, NC) was employed. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. As hs-CRP was not normally distributed, it was logarithmically transformed to more closely reflect a normal distribution when performing linear regression analysis. Relationships were determined using multivariate regression analysis with adjustments for clinic systolic BP, age, sex, waist circumference, HbA1c, regular tobacco intake, regular alcohol intake, pulse rate and treatment for hypertension in the models. To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package).

5.3 Results

5.3.1 Participant characteristics.

The characteristics of those with echocardiography, as well as both CRP and HbA1c measurements were compared to those without both CRP and HbA1c measurements as shown in Table 5.1. No differences were noted between the groups. A high percentage of participants were either overweight or obese. Of the participants 14.1% were either receiving medication for diabetes mellitus or had an HbA_{1C}>6.5%. High sensitivity-CRP concentrations were 6.70±9.46 mg/l.

Table 5.1. Characteristics of participants with echocardiography, with and without C-reactive protein and HbA1c data .

	With (n=361)	Without (n=317)
Sex (% female)	64.3	65.9
Age (years)	43.6±17.8	42.3±17.8
Body mass index (kg/m^2)	29.4±7.5	29.4±8.0
Waist circumference (cm)	90.2±15.7	90.7±17.6
% Overweight/obese	26.6/ 41.3	19.9/ 45.1
Regular tobacco intake (%)	11.4	18.3
Regular alcohol intake (%)	22.7	16.4
Conventional SBP/DBP (mm Hg)	130±21/ 84±12	128±23/ 83±14
% Diabetes mellitus*	14.1	13.3
% Hypertension	46.0	46.4
% Treated for hypertension	22.4	24.3

BP, blood pressure; SBP, systolic BP; DBP, diastolic BP. *Treatment or HbA1c>6.5% (median=3.7, range=0.1-194.9). The % low, moderate, and high risk hs-CRP concentrations was 18.8, 27.2, and 54.0 respectively. In the study sample left ventricular mass (LVM) = 169.8±46.5 g. LVM index = 46.7±12.9 g/m$^{2.7}$, Inappropriate LVM (LVM_{inappr}) = 131.4±24.4%, % LV hypertrophy = 27.4% and % increased LVM_{inappr} = 17.2%.

5.3.2 General factors associated with log hs-CRP.

Age (r=0.36, p<0.0001), sex (r=0.23, p<0.0001), waist circumference (r=0.52, p<0.0001), BMI (r=0.53, p<0.0001), systolic BP (r=0.24, p<0.0001), diastolic BP (r=0.22, p<0.0001), DM or an HbA1c>6.5% (r=0.22, p<0.0001) were correlated with log hs-CRP. In the model with waist circumference only, waist circumference (p<0.0001) and sex (p<0.0005) were correlated with log hs-CRP, and in the model with BMI only, BMI (p<0.0001) and age (p<0.05) were correlated with log hs-CRP.

5.3.3 Relationships between CRP and LVM.

On bivariate (Figure 5.1) and multivariate regression analysis (Table 5.2), CRP was related to LVMI and LVM_{inappr}. Replacing waist circumference with body mass index did not influence the results (Table 5.2).

5.3.4 LVM across quartiles of CRP

With adjustments for confounders LVMI and LVM_{inappr} increased with increasing quartiles of CRP (Table 5.3). The differences in multivariate adjusted LVMI and LVM_{inappr} were noticeable in the fourth as compared to the first quartile of CRP.

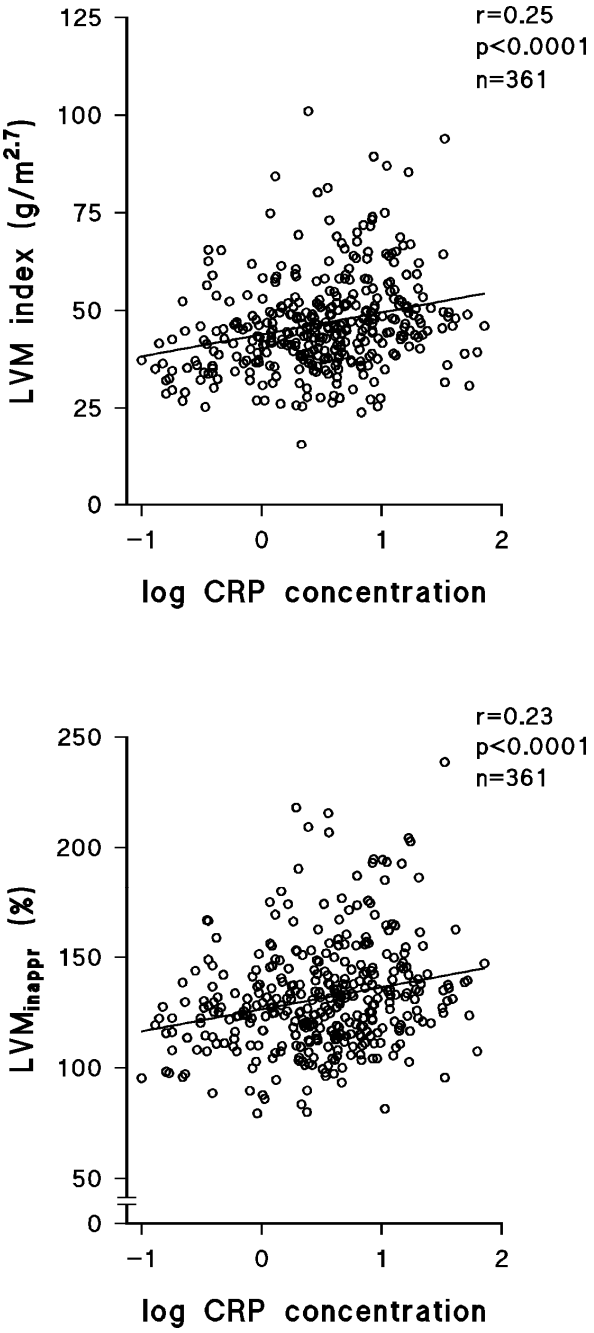

Figure 5.1. Bivariate relationships between log C-reactive protein (CRP) concentration and left ventricular mass (LVM) index or inappropriate LVM (LVM_{inappr}) in a community sample. See Table 5.2 for multivariate adjusted relationships.

Table 5.2. Multivariate adjusted (Partial r) relationships (correlation coefficients [95% confidence intervals]) between plasma C-reactive protein (CRP) concentrations and left ventricular mass index (LVMI) or inappropriate LVM (LVM_{inappr}) in a community sample.

CRP versus	Adjustments	Partial r	CI	p value[†]
		<u>All participants</u> (n=361)		
LVMI	*	0.14	0.03 to 0.24	<0.01
LVMI	*+ waist circ.	0.11	0.001 to 0.21	<0.05
LVMI	*+ BW	0.11	0.001 to 0.21	<0.05
LVM_{inappr}	*	0.17	0.06 to 0.27	<0.005
LVM_{inappr}	*+ waist circ.	0.11	0.001 to 0.21	<0.05
LVM_{inappr}	*+ BW	0.10	0.002 to 0.21	<0.05

Waist circ., waist circumference; BMI, body mass index. *Adjustments are for age, sex, clinic systolic blood pressure, HbA1c (in all participants), pulse rate, regular tobacco use, regular alcohol intake, treatment for hypertension, and either waist circumference or body weight (BW) as indicated. [†]Probability values were further adjusted for non-independence of family members. #Defined as treatment for diabetes mellitus or an HbA1c>6.5%.

Table 5.3. Unadjusted and multivariate adjusted left ventricular mass index (LVMI) or inappropriate LVM (LVM_{inappr}) at increasing quartiles of plasma C-reactive protein (CRP) concentrations in a community sample (n=361).

Quartiles (n)	1 (n=90)	2 (n=90)	3 (n=91)	4 (n=90)	p-values (versus quartile 1)†		
CRP range (mg/l)	<1.31	1.32-3.56	3.57-8.09	≥8.10	2 vs 1	3 vs 1	4 vs 1
CRP (mg/l)	0.67±0.37	2.37±0.59	5.28±1.34	18.42±12.64			
Unadjusted LVMI ($g/m^{2.7}$)	42.5±10.7	44.5±12.4	48.4±14.1	51.5±14.9	=0.32	<0.005	<0.0001
Multivariate adjusted* LVMI ($g/m^{2.7}$)	45.0±11.0	44.6±10.3	46.3±10.0	48.8±10.7	=0.81	=0.43	<0.05
Unadjusted LVM_{inappr} (%)	124±19	127±26	133±24	140±28	=0.38	<0.02	<0.0001
Multivariate adjusted* LVM_{inappr} (%)	127±24	129±23	131±22	137±28	=0.71	=0.29	<0.02

*Adjustments are for age, sex, clinic systolic blood pressure, waist circumference, pulse rate, regular tobacco use, regular alcohol intake, HbA1c, and treatment for hypertension. †Probability values were further adjusted for non-independence of family members.

5.4 Discussion

The main findings of the present study are that in a randomly selected community sample of African ancestry, CRP concentrations were associated with LVMI and LVM_{inappr} independent of co-morbidities. This translated into a markedly higher multivariate adjusted LVM in the fourth as compared to the first quartile for CRP.

Although previous studies have demonstrated relationships between CRP and LVM or LVH, these studies have been conducted in select clinical populations (Pedrinelli et al 2004, Conen et al 2006, Iwashima et al 2007, Assadi et al 2007, Ratto et al 2007, Assadi et al 2008, Masugata et al 2011, Torun et al 2012, Salles et al 2007, Fertin et al 2010, Kim et al 2005, Shi et al 2010, Monfared et al 2013), or in population samples with a low prevalence of risk-related CRP concentrations, where these relationships were not demonstrated to be independent of co-mordities (Mehta et al 2007, Palmieri et al 2003, Arnett et al 2011). Indeed, in a previous study conducted in a 1299 participants of a population sample, an increased LVM was noted with increasing CRP concentrations, but this was only in participants with type II diabetes mellitus, and these relationships were accounted for by an increased BMI (Palmieri et al 2003). Moreover, in the Multiethnic Study of Atherosclerosis conducted in 4973 participants of a population sample, CRP concentrations were directly correlated with LVM, but after adjusting for body weight, an inverse relationship was noted (Arnett et al 2011). In that study the mean log CRP concentrations (mg/l) were 0.80±1.20, -0.02±1.03, 1.09±1.15, 0.99±1.06 for women and 0.24±1.03, -0.13±1.01, 0.53±1.12, 0.59±0.59 for men in Caucasian, Chinese, African and Hispanic participants respectively (Arnett et al 2011). Furthermore, in the Dallas Heart Study conducted in 2633 randomly selected participants the relationship between circulating CRP concentrations and LVM was largely determined by co-morbidities including BMI, hypertension and diabetes mellitus (Mehta et al 2007). In that study the median CRP concentrations were 3.1, 3.5, 3.5, 4.9 mg/l and 4.2, 5.6, 6.9, 7.2 mg/l for quartiles 1 to 4 in men and women respectively (Mehta et al 2007). In contrast, in the

present study conducted in a 361 randomly selected participants from a community-based sample with a high prevalence of circulating CRP concentrations that are consistent with a high risk for cardiovascular disease (54.0% of the sample had high risk concentrations) and where the mean CRP concentrations were higher (6.7±9.46mg/l) than previous studies, I show that CRP concentrations are associated with LVMI or LVM_{inappr} independent of co-morbidities, including increases in waist circumference (or BMI), BP, regular smoking or blood glucose control.

It may be argued that as CRP was strongly associated with BP on bivariate analysis, that residual confounding effects of hypertension may explain the relationships between CRP and LVM, effects which may not necessarily be accounted for by adjustments for BP. In this regard, because few normotensives were obese (29.7% vs 54.8% of hypertensives), normotensives had considerably lower CRP concentrations than hypertensives (43.6% with CRP concentrations consistent with high risk vs 66.3% of hypertensives with high risk CRP concentrations). Thus, I was not statistically powered to evaluate the relationships between CRP and LVMI in normotensives alone. However, if residual confounding effects of hypertension were to explain the independent relationships between CRP and LVM in the community at large, then one would expect BP to be related to CRP in a multivariate model. In contrast, with adjustments for age and adiposity indices, CRP did not retain independent relationships with BP (partial r= -0.005, p= 0.93). Thus, it is unlikely that the relationship between CRP and LVM can be accounted for by the impact of CRP on BP and a consequent effect of BP on LVM.

Although in the present study I was unable to show a significant independent relationship between CRP and LVMI (p=0.08) in the participants without diabetes mellitus, I was nevertheless able to show an independent relationship between CRP and LVM_{inappr}. In this regard, LVM_{inappr} is thought to represent the effect of factors other than sex, height and the principle haemodynamic changes that determine variations of LVM at a population level (the product of systolic BP and stroke volume [stroke work]). It is

therefore likely that the use of LVM_{inappr} rather than LVMI better detects relationships between non-haemodynamic factors, such as CRP, and LVM.

Although in the present study the independent relationships between CRP and LVMI may be considered as weak (partial r=0.11), the clinical significance of these relationships are striking when one compares the multivariate-adjusted LVMI or LVM_{inappr} values in the fourth and the first quartiles (~ 4 $g/m^{2.7}$ difference). Importantly, I cannot exclude the possibility that colinearity between adjustors (i.e. age, waist circumference, systolic BP, diabetes mellitus) may have produced over-adjustment and artificially reduced the strength of the correlations. Only intervention studies designed to specifically target inflammatory changes will answer the question of the actual extent to which CRP may contribute toward variations in LVM at a community level independent of co-morbidities. As such approaches have not been developed for clinical use, this study is unlikely to be forthcoming in the near future.

The clinical implications of the present study relate in-part to the potential use of CRP to assist in predicting LVH. In this regard, several studies have been conducted to assess the diagnostic value of CRP for LVH detection (Pedrinelli et al 2004, Conen et al 2006, Kim et al 2005, Salles et al 2007, Shi et al 2010). Indeed, higher CRP concentrations (CRP > 4.2 mg/L [range: 2.3 – 20.7 mg/L], together with an increased urinary albumin excretion [UAE] > 27 μg/minute [range: 15 – 170 μg/minute]) is associated with a much greater prevalence of LVH (79%) than in individuals without renal impairment and low grade inflammation (median CRP = 1.0 mg/L [range: 0.1 – 2.2 mg/L], median UAE = 6 μg/minute [range: 2 – 14 μg/minute], LVH = 58%) (Pedrinelli et al 2004). Moreover, in hypertensive patients attending an outpatient's department (n = 320), serum CRP concentrations were noted to provide a high degree of sensitivity (68%), a relatively low degree of specificity (59%), but with a significant performance (area under the receiver operating curve [AUC] =0.616) for LVH detection (Conen et al 2006). However, the low specificity for LVH detection previously demonstrated (Conen et al 2006) is of concern, as LVH detection for risk assessment, for example with ECG criteria, was

originally designed to be highly specific. Whether CRP may be employed to complement ECG criteria for LVH detection in communities where ECG criteria alone have a limited specificity, requires further study.

The limitations of the present study have largely been acknowledged in chapter 4. The present study was a cross-sectional design and hence conclusions regarding cause and effect cannot be drawn. Whether CRP is causally related to an increased LVM requires prospective evaluation. Second, a high proportion of participants were women and I was not statistically powered to perform sex-specific analyses. Third, I assessed relationships between CRP and LVM in one ethnic group only. Hence, further studies are required to assess the consistency of the present findings in alternative ethnic groups with a high prevalence of risk-related CRP concentrations.

In conclusion, the results of the present study conducted in a randomly selected community sample indicate that serum CRP concentrations are indeed associated with LVM independent of co-morbidities. Whether CRP may be employed to enhance the sensitivity, specificity or performance of ECG criteria for LVH detection requires further study.

CHAPTER 6

Estimated Glomerular Filtration Rate and C-Reactive Protein Enhance the Specificity for Left Ventricular Hypertrophy Detection of Electrocardiogram Criteria.

Abstract

Whether the use of estimated glomerular filtration rate (eGFR) or C-reactive protein (CRP) concentrations, which are independently associated with LV mass, may complement electrocardiographic (ECG) criteria to improve the specificity or performance for LV hypetrophy (LVH) detection, is uncertain. In 358 participants from a randomly selected community sample with a high prevalence of obesity (41.1%), I evaluated the sensitivity, specificity and performance (area under the receiver operating curves [AUC]) of ECG criteria alone or in combination with values for eGFR below and/or CRP above the median for the sample. Sokolow-Lyon criteria showed negligible performance and Cornell voltage or time-voltage criteria showed a very low sensitivity for LVH detection (11 - 14%). RaVL (and criteria that employ limb-lead recordings only for LVH detection) showed significant performance (AUC=0.70±0.03, $p<0.0005$), but a very low specificity for LVH detection (79%). A combination of CRP concentrations above and eGFR below the median for the sample showed significant performance (AUC=0.61±0.03, $p<0.0005$), but a low specificity for LVH detection (77%). However, when eGFR and CRP concentrations were employed to complement RaVL, although the overall performance did not improve (AUC=0.71±0.03, $p<0.0001$), the specificity increased (93%) whilst sensitivity (25%) was in-line with previously reported sensitivities for LVH detection using ECG criteria in alternative population samples. Without changing overall performance, eGFR together with RaVL increased the specificity to 88% and CRP concentrations when considered together with RaVL increased the specificity to 87%. In conclusion, in a community sample where the specificity and performance of ECG criteria for LVH detection are poor, the use of eGFR and/or CRP concentrations to complement ECG criteria increase the specificity without altering the overall performance.

6.1 Introduction

Left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular outcomes (Casale et al 1986, Levy et al 1990a, Koren et al 1991, Levy et al 1994, Verdercchia et al 1996, Ghali et al 1998, Devereux et al 2004, Okin et al 2004a) and as such the electrocardiographic (ECG) identification of LVH is recommended by all hypertension guidelines for routine risk prediction. However, the value of ECG criteria for the detection of LVH in the obese (Levy et al 1990b, Devereux et al 1983, Rautaharju et al 1994, Abergel et al 1996, Okin et al 1996a, Okin et al 1996b, Okin et al 2000) and in those of black African ancestry (Vanezis and Bhopal 2008, Jaggy et al 2000) is considerably reduced. Moreover, in obese individuals of African descent none of the currently recommended criteria for LVH detection can be employed either because of negligible performance of these criteria or because specificity values are considerably reduced (Maunganidze et al 2013a, chapter 3). Whether alternative approaches that are relatively easily accessible (echocardiography or more sophisticated measures of LVH detection are not easily accessible), such as blood markers associated with LVH, can be used to either replace or complement current ECG criteria is uncertain.

A number of blood markers may be obtained as part of clinical assessment which could be used to detect LVH. In this regard, estimated glomerular filtration rate (eGFR) is strongly and independently associated with LV mass index (LVMI)(Maunganidze et al 2013b, chapter 4). Moreover, a number of studies have provided evidence to suggest that blood concentrations of the inflammatory marker, C-reactive protein (CRP), are associated with LVMI or LVH (Pedrinelli et al 2004, Conen et al 2006, Masugata et al 2011, Salles et al 2007, Fertin et al 2010, Kim et al 2005, Shi et al 2010, Mehta et al 2007, Palmieri et al 2003, Maunganidze et al [chapter 5]) and these relationships are independent of comorbid conditions (Maunganidze et al [chapter 5]). However, serum CRP concentrations may provide a high degree of sensitivity (68%), but a low degree of specificity (59%) for LVH detection (Conen et al 2006). What has not been addressed is

whether blood markers may be employed to complement ECG criteria for LVH detection. Hence, in the present study I evaluated whether eGFR and serum CRP concentrations may be employed to complement current ECG criteria to improve either the overall performance or the specificity for LVH detection.

6.2 Methods

6.2.1 Study participants

The study participants were recruited as described on pages 56 to 57, in section 2.2.1 of chapter 2 of the present thesis. Of the 678 participants enrolled in an echocardiographic substudy, 358 participants had measures of blood high sensitivity CRP (hs-CRP) concentrations and percentage glycated haemoglobin (HbA1c) as well as eGFR assessments.

6.2.2 Clinical, demographic, and anthropometric measurements

Clinical and demographic data were obtained using a standardised questionnaire as described on pages 57 to 58 in section 2.2.2 of chapter 2 of the present thesis. Anthropometric data was obtained also as described on pages 57 to 58, in section 2.2.2 of chapter 2 of the present thesis. Participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2.

6.2.3 Blood collection and analysis

Blood analysis was performed as described on pages 58 to 59 in section 2.2.3 of chapter 2 of the present thesis. Ultrasensitive-CRP (hs-CRP) concentrations were determined as described on pages 123 to 124 in section 5.2.3 of chapter 5 of the present

thesis. Estimated GFR was calculated as described on page 95 in section 4.2.6 of chapter 4 of the present thesis.

6.2.4 Conventional blood pressure

Conventional (brachial) blood pressure (BP) measurements were performed as described on page 59 to 60 in section 2.2.4 of chapter 2 of the present thesis. The quality control criteria for the present study are given on page 124 in section 5.2.4 of chapter 5 of the present thesis.

6.2.5. Electrocardiography.

A standard 12-lead ECG was recorded using the Philips, Pagewriter Trim II, as as described on pages 60 to 61 in section 2.2.5 of chapter 2 of the present thesis. All the ECG criteria for LVH were calculated using standard formulae. Thresholds (cut-points) of ECG criteria for LVH were determined as described on page 80 in section 3.2.5 in chapter 3 of the present thesis.

6.2.6. Echocardiography

Echocardiographic measurements were performed using two-dimensional targeted M-mode echocardiography as described on pages 62 to 64 in section 2.2.6 of chapter 2 of the present thesis. Thresholds of LVMI for LVH detection are given on pages 62 to 64 in section 2.2.6 of the present thesis.

6.2.7. Data analysis

Statistical analysis and database management were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). Continuous data are reported as

mean ± SD or mean ± SEM. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. The performance of each the different ECG criteria for LVH detection was compared to that of echocardiographic LVH detection. Sensitivity and specificity of ECG criteria for LVH detection were determined using standard approaches. The performance of ECG criteria for LVH detection was determined from the area under the receiver operating characteristic (ROC) curves (area under the curve [AUC]).

6.3 Results

6.3.1 Participant characteristics.

As only 3 participants from the present study are not represented in the data shown in chapter 5, participant characteristics are largely those shown in Table 5.1 on page 126. Hence, these characteristics will not be shown again or further discussed. High sensitivitys-CRP concentrations were 6.55±9.32 mg/l. Estimated GFR was 104.7±26.6 ml/min/1.73m^2.

6.3.2 Comparison of sensitivity, specificity and performance of ECG criteria, eGFR and CRP for LVH detection.

Table 6.1 compares the sensitivity, specificity and performance for LVH detection using currently recommended ECG criteria, and eGFR or CRP concentrations below and above the median for the sample respectively. Cornell voltage and time voltage criteria as well as those ECG criteria which include limb-lead recordings alone showed a significant level of performance for LVH detection (Table 6.1). In contrast, the Sokolow-Lyon criteria failed to show significant performance for LVH detection (Table 6.1). Importantly, the specificity for LVH detection using criteria that employ limb-lead recordings only was 78.9 to 80.8% and the sensitivity for Cornell criteria was only 11 – 14%.

Table 6.1. Comparison of the sensitivity, specificity and performance (area under the receiver operating curves-AUC) of electrocardiographic predictors of left ventricular hypertrophy (left ventricular mass indexed to height$^{2.7}$>51 g/m$^{2.7}$)(LVMI) versus alternative clinical indices of LV hypertrophy.

Increased LVMI vs	Threshold	Sensitivity (%)	Specificity (%)	AUC±SEM
RaVL	>0.73 mV	39	79	0.70 ±0.03**
Cornell voltage	>3.17 mV	11	95	0.63 ±0.03*
Sokolow-Lyon voltage	>4.63 mV	0	100	0.53 ±0.03
Gubner-Ungerleider voltage	>1.50 mV	42	81	0.66 ±0.03**
Lewis voltage	>1.17 mV	44	80	0.68 ±0.03**
Cornell time-voltage product	>281 mV	14	94	0.64 ±0.03*
Sokolow-Lyon time-voltage product	>405 mV	5	92	0.56 ±0.03
Gubner-Ungerleider time-voltage product	>125 mV	42	79	0.65 ±0.03**
eGFR (ml/min/1.73m^2)	<100.29	63	55	0.61 ±0.03*
C-reactive protein (mg/ml)	> 3.42	65	56	0.61 ±0.03*

eGFR, Estimated glomerular filtration rate; * p<0.05, ** p<0.0005 indicates significance of AUC.

Participants with either an eGFR below the median or a CRP concentration above the median for the sample also showed significant levels of performance for LVH detection, but both measures showed a low level of specificity (55-56%). A combination of a eGFR below the median and a CRP concentration above the median for the sample improved the specificity (77%), although the final specificity was still suboptimal.

6.3.3 Impact of adding eGFR and CRP to ECG criteria for LVH detection on sensitivity, specificity and performance.

Table 6.2 compares the sensitivity, specificity, negative predictive values (NPV) and performance for LVH detection with eGFR or CRP concentrations below and above the median for the sample respectively added to ECG criteria for LVH detection. Only the effects on those criteria which had a significant level of performance and a low specificity to begin with are shown. Although the addition of eGFR or CRP concentrations below or above the median for the sample failed to modify the overall performance for LVH detection of ECG criteria that incorporate limb-lead recordings only, the specificity improved, but at the expense of a lower senistivity. The addition of both an eGFR below the median and a CRP concentration above the median for the sample achieved a level of specificity and sensitivity of ECG criteria for LVH detection comparable with previously published studies in alternative population samples (Table 1.3.).

6.4 Discussion

The main findings of the present study are as follows: In a population sample where ECG criteria generally show either a poor level of performance, a low sensitivity or a low specificity for LVH detection, eGFR values below the median for the sample and CRP concentrations above the median for the sample demonstrated a significant and equivalent level of performance for LVH detection, but also with a low level of specificity.

Table 6.2. Impact on the sensitivity, specificity and performance (area under the receiver operating curves-AUC) of electrocardiographic predictors of left ventricular hypertrophy (left ventricular mass indexed to height$^{2.7}$>51 g/m$^{2.7}$)(LVMI) with the addition of alternative clinical indices of LV hypertrophy.

Additions	eGFR < 100.29 alone				CRP > 3.42 alone				eGFR < 100.29 + CRP> 3.42			
Increased LVMI vs	Sens (%)	Spec (%)	NPV (%)	AUC±SEM	Sens (%)	Spec (%)	NPV (%)	AUC±SEM	Sens (%)	Spec (%)	NPV (%)	AUC±SEM
RaVL	29	88	78.3	0.71±0.03*	33	87	77.9	0.70±0.03*	25	93	88.6	0.71±0.03*
Gubner-Ungerleider voltage	32	89	77.1	0.69±0.03*	34	89	76.7	0.66±0.03*	26	94	79.8	0.67±0.03*
Lewis voltage	33	88	78.1	0.68±0.03*	34	89	77.5	0.68±0.03*	26	94	82.1	0.68±0.03*
Gubner-Ungerleider time-voltage product	31	89	76.7	0.66±0.03*	34	89	74.9	0.65±0.03*	26	95	78.9	0.66±0.03*

* p<0.0005 indicates significance of AUC. NPV – negative predictive value; AUC – area under the curve

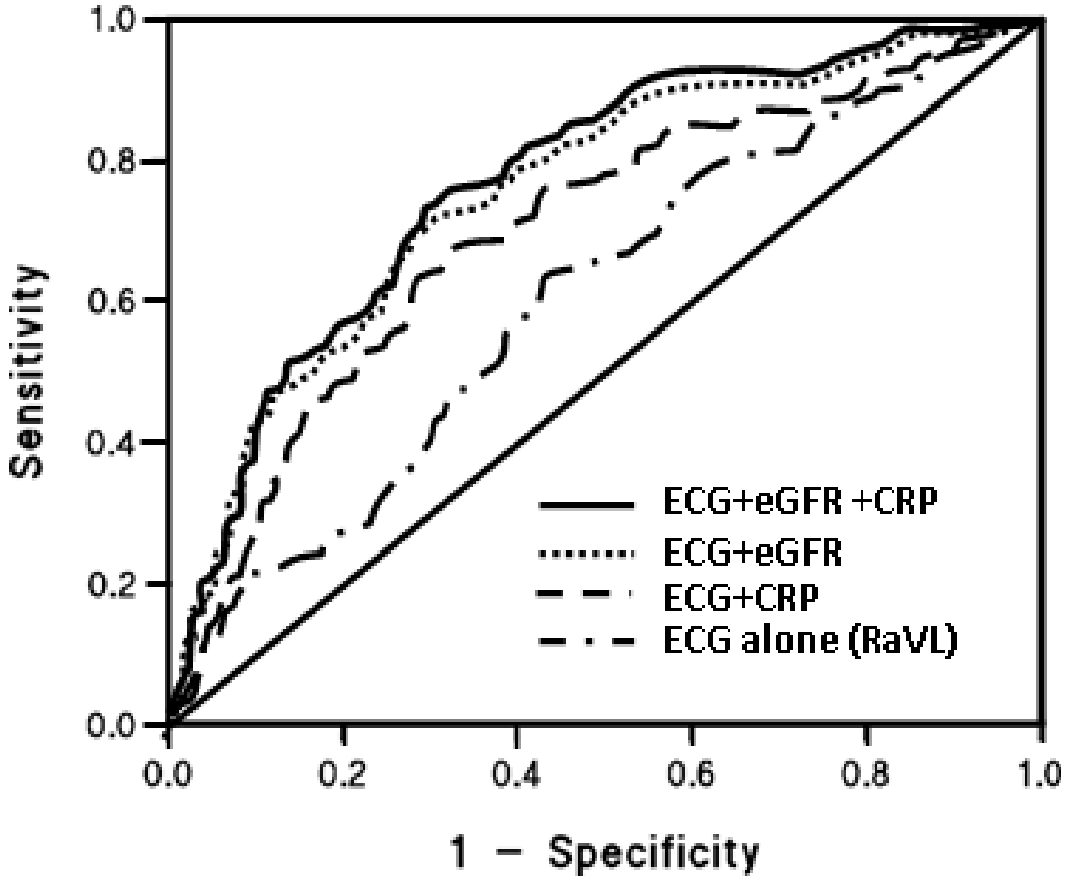

Figure 6.1 ROC curves showing the incremental area under the curve (AUC) when ECG (RaVL criterion) is used together with CRP (ECG + CRP), eGFR (ECG + eGFR) and both (ECG + CRP + eGFR).

However, the addition of eGFR and CRP thresholds to ECG criteria with initial low specificities, improved specificity without modifying overall performance.

As with the present study where CRP thresholds were noted to provide a high degree of sensitivity (65%) and low degree of specificity (56%), with a significant performance for LVH detection, previous studies have similarly demonstrated that thresholds for serum CRP concentrations may provide a high degree of sensitivity (68%), but a low degree of specificity (59%) for LVH detection (Conen et al 2006). However, the present study extends these previous findings to show that thresholds for eGFR similarly provide a high degree of sensitivity (63%) and low degree of specificity (55%), with a significant performance for LVH detection. Moreover, the combination of these criteria (eGFR and CRP) improved the specificity (77%) at the expense of a lower sensitivity (44%), whilst maintaining performance (AUC=0.61±0.03).

Importantly, the addition of eGFR and CRP criteria to the best performing ECG criteria (criteria which incorporate limb-lead recordings only), produced a level of specificity (95 - 93%) and corresponding sensitivities (25 - 26%) for LVH detection that can be considered comparable with alternative studies with large or relatively large sample sizes (n>300) that have reported on the sensitivity and specificity of the best ECG criteria for LVH detection. In this regard, in studies with a sample size>300, the widely regarded Sokolow-Lyon voltages have been demonstrated to show sensitivities of 8-28% at corresponding specificities of 97-96% for LVH detection (Schillaci et al 1994, Crow et al 1995, Chapman et al 1999, Verdecchia et al 2000, Jaggy et al 2000, Sundstrom et al 2001, Salles et al 2005, Mazzaro et al 2008, Casiglia et al 2008, de Costa et al 2008, Rodriguez-Pedial et al 2012, Gosse et al 2012), whilst one study showed a sensitivity of 43% at a specificity of 96% (Okin et al 1995a). In addition, in studies with a sample size>300, the similarly widely regarded Cornell voltages or time-voltage criteria showed sensitivities of 3.8-28% at corresponding specificities of 97.6-96% for LVH detection (Schillaci et al 1994, Crow et al 1995, Okin et al 1995a, Chapman et al 1999, Verdecchia et al 2000, Jaggy et al 2000, Sundstrom et al 2001, Salles et al 2005, Mazzaro et al 2008,

Casiglia et al 2008, de Costa et al 2008, Rodriguez-Pedial et al 2012, Gosse et al 2012). In addition, in studies with a sample size >300, criteria which employ limb-lead recordings such as Lewis and Gubner Ungerleider voltages show sensitivities of 3.8-24% at corresponding specificities of 97.6-89% (Schillaci et al 1994, Okin et al 1995a, Verdecchia et al 2000, Jaggy et al 2000, Casiglia et al 2008, Rodriguez-Pedial et al 2012). Furthermore, in studies with a sample size>300 which assessed RaVL alone, showed sensitivities of 5.2-20% at corresponding specificities of 92-96% (Schillaci et al 1994, Okin et al 1995a, Casiglia et al 2008, de Costa et al 2008, Rodriguez-Pedial et al 2012, Gosse et al 2012).

Whether at a clinical level, assessments of eGFR and serum CRP concentrations should be added to current ECG criteria for LVH detection requires a considerable amount of further study. In this regard, the current study was not an outcomes-based study. Indeed, ECG criteria have been incorporated into risk assessment based on data that show that these criteria predict cardiovascular events. A similar approach would be required before eGFR+CRP+ECG criteria together can be similarly incorporated into risk prediction charts. However, the current data suggest that in populations where ECG criteria show a considerably poor performance sensitivity or specificity for LVH detection, that estimations of eGFR, which are recommended by all guidelines, may be employed together with ECG criteria, to determine whether patients should be referred for echocardiography. In addition, in those centres that recommend CRP measurements, these measurements may also be evaluated together with ECG criteria to determine whether patients should be referred for echocardiography. Using these approaches could considerably limit the excessive cost and over-use of resources required to perform echocardiography on all patients whom may have LVH, but are likely to have ECG measurements which provide a limited utility for LVH detection.

The limitations of the present study include the following. In the present study the limited number of participants with CRP measurements did not allow me to assess the combined effect of ECG criteria, together with eGFR and CRP thresholds for LVH

detection in obese participants alone. In this regard, further studies are warranted to confirm that this combination of criteria enhance the specificity for LVH detection without compromising performance in the obese. Moreover, in the present study the limited number of male participants did not allow for sex-specific analysis and hence the results of the present study may relate specifically to females.

In conclusion, in a population sample where ECG criteria generally show a poor level of performance and a low specificity for LVH detection, eGFR values below the median for the sample and CRP concentrations above the median for the sample when employed together with ECG criteria which employ limb-lead recordings alone, increase the specificty for LVH detection without compromising on performance. The achieved levels of specificity (95 - 93%) at corresponding sensitivities (25 - 26%) are comparable with studies that have reported on sensitivity and specificity for the best ECG criteria in population samples where these criteria are not limited in their use. These data suggest that eGFR assessments and CRP measurements may complement ECG criteria for LVH detection.

CHAPTER 7

Summary and Conclusions

The recognition of an emergence of cardiovascular disease as a major cause of death and disability in both developed and developing (Kahn et al 2000, Pearson 1999, Yusuf et al 2001, Ebrahim and Smith 2001, Reddy 2002, Boutayeb 2006) countries emphasises the need for effective programmes designed to estimate the risk for cardiovascular disease in order to institute appropriate interventions in all countries world-wide. It is now well recognised that appropriate risk assessment should not rely only on the use of traditional risk factors to assess overall (global) risk. In this regard, it is well-established that cardiovascular target organ damage detected prior to the development of cardiovascular events reflects the combined impact of a number of traditional risk factors accrued over time as well as the adverse effects of a number of non-traditional risk factors. In this regard as discussed in chapter 1, electrocardiographic (ECG) or echocardiographic assessments for LVH provide some of the best independent predictions of cardiovascular outcomes (see chapter 1 for review). Indeed in the management of hypertension, regression of LVH has been associated with a reduced risk for cardiovascular disease with improved outcomes (see chapter 1 for review). The ECG assessment of LVH has therefore been recommended for routine risk assessment in the 2007 guidelines of the European Society of Hypertension and European Society of Cardiology (Mancia et al 2007) and in the Southern Africa Hypertension Society guidelines (Seedat and Rayner 2012). The use of ECG criteria for LVH detection is preferable to alternative assessments of LVH, such as echocardiography and magnetic resonance imaging especially in developing countries, because it is a rapid and cheap assessment technique, does not inappropriately utilise scarce specialist resources and requires less skill than alternative diagnostic tests. However, with respect to the ability to employ ECG criteria for LVH detection, a number of unanswered questions remain.

In the present thesis I aimed to advance our current knowledge of the importance of obesity in the detection of LVH in groups of African descent. First I assessed the effect of obesity on the ability to employ ECG criteria for LVH detection in a group of African ancestry. Having demonstrated that obesity markedly attenuates the ability to detect LVH

using ECG criteria I subsequently sought to determine whether “biomarkers” associated with LVH may be employed to enhance the ability to detect LVH. In this regard, I first assessed whether early renal dysfunction and markers of obesity-associated inflammation are associated with LVH independent of a number of traditional and non-traditional haemodynamic risk factors and having demonstrated that both of these markers are indeed independently associated with LVH, I subsequently evaluated whether these two markers may be employed to enhance the ability of ECG criteria to detect LVH. The work described in the present thesis has been published in-part in international peer-reviewed journals (Maunganidze et al 2013a, Maunganidze et al 2013b). In the present chapter I will summarise the findings of the present thesis in the context of our existing understanding of the role of ECG assessments for LVH detection and the possible role of the biomarkers evaluated in the present thesis for LVH detection.

7.1 Can current ECG criteria for LVH detection be used in obese individuals in groups of African ancestry?

The ability to detect LVH with ECG asessments is influenced by a number of factors. In this regard ethnicity is one such factor (Ashcroft 1972, Munro-Faure et al 1979, Arnett et al 1992, Lee et al 1992, Sutherland et al 1993, Xie et al 1994, Rautaharju et al 1994, Arnett et al 1994, Chaturvedi et al 1994, Arnett et al 1997, Vanezis and Bhopal 2008, Vitelli et al 1998, Chapman et al 1999, Rautaharju et al 2000, Jaggy et al 2000, Okin et al 2002, Spencer et al 2004, Dada et al 2005, Martin et al 2007, Jain et al 2010). As reviewed in chapter 1, a number of reports have suggested that QRS complex voltages (particularly R_{V5}, R_{aVL} and S_{V1}) are higher in Africans than in Caucasians (Munro-Faure et al 1979, Rautaharju et al 1994, Chaturvedi et al 1994, Vitellli et al 1998, Chapman et al 1999, Spencer et al 2004, Jain et al 2010). Although initially these higher voltages were thought to represent an increased prevalence of LVH, subsequently, it was hypothesised that these effects may be attributed to modifications in skin conductivity

(Krovetz 1994) or a diminished thoracic diameter reducing the distance from the skin surface to the heart (Walker et al 1972, Ashcroft 1972, Horton et al 1977). These hypotheses were introduced to explain the fact that the increased QRS complex amplitudes may translate into a significantly higher prevalence of ECG-detected LVH than echocardiographically-detected LVH (Lee et al 1992, Rautaharju et al 2000); higher values for Sokolow-Lyon and 12-lead criteria for LVH (Okin et al 2002, Rautaharju et al 2000); a poor specificity for Sokolow-Lyon and 12-lead criteria for LVH detection when compared to echocardiograph-detected LVH (Okin et al 2002, Dada et al 2005, Martin et al 2007, Jain et al 2010); and also possibly a poor sensitivity for LVH detection (Jaggy et al 2000, Martin et al 2007) in groups of African decent as compared to Caucasians. In this regard however, ECG criteria for LVH detection have nevertheless also been shown to be more sensitive in groups of African descent (Chapman et al 1999, Jain et al 2010). These differences noted between Caucasians and Africans in ECG criteria for LVH detection has led to considerable uncertainty as to the value of electrocardiography for risk assesment in these ethnic groups.

The ability to detect LVH with ECG asessments is also influenced by obesity (Frank et al 1986, Nath et al 1988, Abergel et al 1996, Okin et al 1996b, Alpert et al 2000, Okin et al 2000, Fraley et al 2005, da Costa et al 2008, Smith et al 2010, Domienik-Karlowicz et al 2011). The presence of obesity may markedly attenuate QRS amplitudes (Frank et al 1986, Alpert et al 2000), particularly over chest leads, and hence diminish the capacity to detect LVH using ECG criteria. This has been postulated to be the result of an increased distance between the precordial leads and the heart due to accumulation of adipose tissue (Nath et al 1988). As a consequence of the reduced QRS amplitudes, particularly over chest lead recordings (Frank et al 1986, Alpert et al 2000), criteria which rely heavily on chest lead recordings such as the Sokolow-Lyon criteria show a negative correlation with indices of adiposity (Okin et al 2000) and a markedly reduced performance and sensitivity for LVH detection (Abergal et al 1996, Okin et al 1996b, da Costa et al 2008). In contrast, criteria which depend more on limb lead QRS amplitudes,

such as RaVL and Cornell voltage criteria are positively correlated with obesity (Okin et al 2000), and have a higher performance and sensitivity for LVH detection in obesity (Nath et al 1988, Abergel et al 1996, Okin et al 1996b, da Costa et al 2008, Smith et al 2010, Dominiek-Karlowicz et al 2011). Obesity nevertheless does not appear to significantly diminish the specificities of ECG criteria for LVH detection, and obesity may not affect the sensitivity of RaVL, Cornell voltage and Cornell product criteria for LVH detection (da Costa et al 2008). However, in the morbidly obese (body mass index [BMI] ≥ 40 kg/m^2; n = 85), the very low sensitivity of 2% at 98% specificity of the Cornell product, suggests that even those criteria which rely more on limb-lead recordings for LVH detection are of little value in these individuals (Domienik - Karlowicz et al 2011).

As both African ancestry and obesity may affect the ability of ECG criteria to detect LVH, the question which arises from this evidence is whether the combined effects of obesity and African ethnicity may render ECG criteria for LVH detection invalid? This question is particularly important given the high prevalence of obesity that exists in this ethnic group in South Africa (Puoane et al 2002). Although one prior study has demonstrated that the left axis shift which occurs in obesity is more pronounced in Africans than in Caucasians (Rautaharju et al 1994), there are no studies that have examined the impact of obesity on ECG criteria for LVH detection specifically in groups of African descent. Therefore, in the present thesis I explored the question of the impact of obesity on ECG criteria for LVH detection in a group of African descent with a high prevalence of obesity. What are these findings and the implications thereof?

As described in chapter 2, in a large study sample (n=661) from a community sample of African ancestry with a high prevalence of obesity (43%), I note that body mass index (BMI) was inversely associated with Sokolow-Lyon (SL) voltage and the SL product as well as the 12 lead QRS voltage sum criteria. Moreover, no relationships between BMI and Cornell voltage or product were noted and although BMI was associated with voltage criteria that incorporate limb lead recordings only, these relationships were not as strong as BMI-LV mass index relations. Moreover, no relationships between SL or 12 Lead QRS

sum criteria and LVMI were noted, the strength of the correlation between RaVL and LVMI was reduced in obese as compared to non-obese participants. These data therefore suggested that in groups of African ancestry with a high prevalence of obesity, neither SL nor Cornell criteria should be employed to detect obesity-induced LVH and the impact of criteria that employ limb lead recordings only, may also be considerably decreased in the obese. These findings were subsequently reported on in-part in a recent publication (Maunganidze et al 2013a). As a consequence of these findings, in chapter 3 I subsequently explored the sensitivity, specificity and overall performnce of the currently employed criteria for LVH detection in this same community sample. What is the impact of obesity on the sensitivity, specificity and performance of ECG criteria for LVH detection in the community studied?

In chapter 3, in the same community-based sample in whom 21.8% of participants had LVH (LVMI>51 $g/m^{2.7}$), although Sokolow-Lyon (SL) voltages and time-voltage product criteria and Cornell voltage criteria showed a significant performance for LVH detection in the non-obese, they failed to show a significant performance in the obese. Moreover, the performance of SL and Cornell criteria was decreased in the obese as compared to the non-obese and the ECG criteria which employ limb-lead recordings only (e.g. RaVL) showed a reduced performance in the obese as compared to the non-obese and a markedly reduced specificity for LVH detection in the obese (76%) than the non-obese (92%, $p<0.0001$) despite similar sensitivities (32% vs 30%). Similar differences in performance, sensitivity and specificity for LVH detection were noted for alternative criteria that employ limb lead recordings only. These findings were largely reproduced in sensitivity analysis conducted in groups with or without diabetes mellitus or a poor blood glucose control. Thus, in chapter 3 I provide the evidence to suggest that in groups of African ancestry, none of the current ECG criteria for LVH detection can be recommended for use in obesity. These findings were subsequently reported on in-part in a recent publication (Maunganidze et al 2013a). This obviously means that the current guidelines

for the assessment of LVH in this population need revision and that alternative cost effective approaches to diagnosing LVH need to be explored.

7.2 Implications and potential solutions to the problem that ECG criteria for LVH detection cannot be recommended for use in obese individuals in groups of African ancestry

The inability to appropriately detect LVH using ECG criteria in obese individuals of African descent living in Africa has major implications for these communities. As previously reviewed in chapter 1, individuals of African decent have a higher prevalence of LVH (Koren et al 1993, de Simone et al 1994, Gardin et al 1995, Zabalgoitia et al 1998, Skelton et al 2003, Kizer et al 2004, Rodriguez et al 2004, Drazner et al 2005), a greater susceptibility to the adverse effects of BP on LVM (Hammond et al 1984, Xie et al 1994, Harris et al 2000), an earlier onset of a high BP, and a 2-3 times higher LVH prevalence than Caucasians (Beaglehole et al 1975). Moreover, the prevalence of obesity in South Africans of African ancestry is remarkably high (Puoane et al 2002) and as previously demonstrated by our group, a strong and independent relationship (beyond all haemodynamic factors) exists between an excess adiposity and LVH in groups of African ancestry in South Africa (Woodiwiss et al 2008). Thus, an inability to detect LVH using ECG criteria generates a conundrum for appppropriate healthcare delivery. There is no question that using alternative methods of detecting LVH, such as echocardiography or magnetic resonance imaging (MRI) is not feasible because of both the cost and resource implications. Therefore, healthcare authorities may choose to either exclude LVH detection from risk assessment in obese Africans, with the obvious implications to this group, or accept that a number of obese individuals will be over-diagnosed with LVH due to the low specificity of the limb-lead recordings, and consequently will receive antihypertensive therapy when not required. Alternatively, other cost-effective approaches may be sought. Indeed, in the present thesis I evaluated whether measures of estimated

glomerular filtration rate (eGFR) and/or C-reactive protein (CRP) concentrations may be employed to complement ECG criteria for LVH detection. Since serum creatinine concentrations are routinely measured in clinical practice at an affordable cost, the use of eGFR in the assessment of cardiovascular risk would have no further cost implications to the patient or the health delivery system. Moreover, the additional measurement of CRP to be used together with ECG and eGFR would not be as expensive as the alternative diagnostic measures (echocardiography and MRI) that may be needed to exclude the presence of LVH.

7.3 Can estimated glomerular filtration rate and C-reactive protein be employed as potential "biomarkers" of LVH?

Generally the term "biomarker" is employed to refer to the concentrations of a substance in the blood that is released from an organ when that organ is damaged or when it is enlarged. Good examples of this for the heart are brain-natriuretic hormone, troponin T, and creatinine kinase isoenzymes. Although in subsequent discussion I have employed estimated glomerular filtration rate (eGFR) and C-reactive protein (CRP) concentrations in a similar manner as other "biomarkers", they are not in the strictest sense biomarkers as neither creatinine concentrations (employed to estimate eGFR) nor CRP concentrations are derived from the LV. However, both of these measurements are often routinely measured when risk predicting. As such, the use of these measurements to complement ECG criteria for risk prediction will cost nothing more, whilst the use of biomarkers derived from the heart will in most circumstances incur additional costs and these costs may be considerable. The use of eGFR and CRP measurements are supported by a number of studies that have demonstrated associations between eGFR or CRP and LVM. However, for both of these measurements, prior to the present thesis a number of issues were outstanding with respect to these relationships. As a consequence in the present thesis I further explored these issues before evaluating their possible role in

LVH detection. What are these issues and how has the present thesis contributed toward our understanding of these issues?

Prior to the present thesis a number of studies had established a relationship between renal impairment and left ventricular mass (LVM) independent of conventional BP and long before the development of overt renal failure (Levin et al 1996, Landray et al 2001, Leoncini et al 2003, Leoncini et al 2004, Henry et al 2005, Paoletti et al 2005, Leoncini et al 2008, Nardi et al 2009, Leoncini et al 2009, Cerasola et al 2010, Masugata et al 2010, Cioffi et al 2011). However, these studies had largely been conducted in select clinical samples of which 66-100% of participants were either hypertensive or had a history of hypertension. Residual confounding long-term haemodynamic effects produced by hypertension may therefore explain these relations. Moreover, arterial stiffness had previously been reported to account for associations between early renal impairment and LVM (Henry et al 2005) and with adjustments for 24-hour BP, only a trend ($p<0.05$) for a relationship between early renal impairment and LVM persisted (Cerasola et al 2010). Prior to the present thesis it was therefore possible that the relationships between early renal impairment and LVM may be entirely explained by haemodynamic factors and hence may not add to the use of BP or alternative haemodynamic measurements to detect LVH. To caste further light on this issue, in the present thesis I assessed associations between early renal impairment and LVM in a community rather than in a hypertensive sample, and the extent to which these relations are determined by haemodynamic factors. What are the results of this study and what are the implications of these results?

So in chapter 4, I describe in 621 randomly selected participants from a community sample (332 were normotensive) that with adjustments for confounders (including clinic systolic BP) eGFR was strongly and inversely associated with LVM index and LVM in excess of that predicted from stroke work (inappropriate LVM, LVM_{inappr}) in all participants and normotensives separate from hypertensives. Marked differences in LVM_{inappr} were noted in the eGFR range <132 compared to ≥132 mls/min/1.73m^2 ($p<0.0005$). When

replacing clinic BP with either aortic systolic BP, 24-hour BP, PWV, stroke work (for LVMI), LV end diastolic diameter (LVEDD), or circumferential wall stress in the regression models, eGFR retained strong associations with LVMI and LVM_{inappr} and these effects were also replicated in normotensives separate from hypertensives. These data therefore provided strong evidence that relationships between eGFR and LVM occur at a community level irrespective of the presence of hypertension and independent of 24-hour and aortic BP, PWV, LVEDD, stroke work and wall stress. These results therefore suggested that non-haemodynamic factors explained a considerable proportion of the relationship between early glomerular dysfunction and LV hypertrophy. As a consequence, this study suggested that eGFR may be employed as a marker of LVH beyond that of traditional or alternative haemodynamic factors. Hence, I selected eGFR as one possible marker that may complement ECG criteria for LVH detection. However, I also considered the usefulness of CRP as a possible marker that may complement ECG criteria for LVH detection either alone or together with eGFR. Nevertheless, prior to the present thesis, the extent to which CRP concentrations were correlated with LVM independently of confounders was uncertain. What are these uncertainties and how have the results of the present thesis addressed these issues?

Prior to the present thesis CRP concentrations had been associated with LVM or LVH in the general population (Mehta et al 2007, Arnett et al 2011), in type II diabetes mellitus (Palmieri et al 2003), in hypertensives (Pedrinelli et al 2004, Conen et al 2006, Iwashima et al 2007, Assadi et al 2007, Ratto et al 2007, Assadi et al 2008, Masugata et al 2011, Torun et al 2012), in resistant hypertensives (Salles et al 2007), in patients hospitalised for myocardial infarction (Fertin et al 2010), in end-stage renal disease (Kim et al 2005, Monfared et al 2013), and in systemic lupus nephritis (Shi et al 2010). However, relationships reported on in these select clinical samples (Pedrinelli et al 2004, Conen et al 2006, Iwashima et al 2007, Assadi et al 2007, Ratto et al 2007, Assadi et al 2008, Masugata et al 2011, Torun et al 2012, Salles et al 2007, Fertin et al 2010, Kim et al 2005, Shi et al 2010, Monfared et al 2013) may be interpreted as representing the effects

of a selection bias. Moreover, the relationships reported on in population studies (Mehta et al 2007, Palmieri et al 2003, Arnett et al 2011) were attributed to the confounding effects of co-morbidities, including obesity, diabetes mellitus, or hypertension. Indeed, the direct relationships between CRP concentrations and LVH noted in two large population samples (n=2633-4973) was not independent of co-morbidities (Mehta et al 2007, Arnett et al 2011). Furthermore, the relationship between CRP and LVH in an alternative large (n=1299) population sample was only noted in those with type II diabetes mellitus (Palmieri et al 2003). Thus, prior to the present thesis there was uncertainty as to the independent role of CRP in mediating LVH. This uncertainty prompted me in the present thesis to evaluate whether high sensitivity (hs) CRP concentrations are associated with LVM independent of co-morbidities. What are the findings of this study and the potential implications thereof?

In chapter 5 of the present thesis in 361 randomly selected participants from a community with a high prevalence of CRP concentrations considered to be high-risk (54%), but without cardiovascular or renal disease, I showed that serum CRP concentrations were correlated with both LVMI and LVM_{inappr} ($p<0.0001$). With adjustments for a number of potential confounders including age, systolic blood pressure, waist circumference (or body mass index), and glucose control (glycated haemoglobin), the relationships between serum CRP concentrations and both LVMI and LVM_{inappr} (partial $r=0.11$, $p<0.05$ for both) persisted. The independent relationship between CRP and LVMI or LVM_{inappr} translated into a markedly higher multivariate-adjusted LVMI and LVM_{inappr} values in the highest as compared to the lowest quartile of CRP. Thus, in the present thesis I provide the evidence to show that CRP is indeed associated with LVM independent of co-morbidities. As a consequence, this study suggested that serum CRP concentrations may be employed as a marker of LVH beyond that of traditional risk factors. Hence, I selected serum CRP concentrations as another possible marker that may complement ECG criteria for LVH detection.

Having provided evidence to show that either eGFR or CRP are markers of increases in LVM independent of traditional risk factors, the remaining question that I addressed as part of the present thesis was whether these markers could be employed to complement ECG criteria for LVH detection.

7.4 Estimated glomerular filtration rate and C-reactive protein concentrations complement current ECG criteria for LVH detection.

In chapter 6 of the present thesis I report in 358 participants from a randomly selected community sample with a high prevalence of obesity (41%), that Sokolow-Lyon criteria showed negligible performance and Cornell voltage or time-voltage criteria showed very low sensitivity for LVH detection (11-14%). RaVL showed significant performance, but a very low specificity for LVH detection (79%). A combination of CRP concentrations and eGFR above the median for the sample showed significant performance, but a low specificity for LVH detection (77%). However, when eGFR and CRP concentrations were employed to complement RaVL, although the overall performance did not improve, the specificity increased (93%) whilst sensitivity (25%) was in-line with previously reported sensitivities for LVH detection using ECG criteria in alternative population samples. Without changing overall performance, eGFR together with RaVL increased the specificity to 88% and CRP concentrations when considered together with RaVL increased the specificity to 87%. Thus, in this study I was able to demonstrate that in a community sample where the specificity and performance of ECG criteria for LVH detection are poor, the use of eGFR and/or CRP concentrations to complement ECG criteria increases the specificity without altering the overall performance. When I considered the cost saving of adding the eGFR and/or CRP concentrations to complement ECG criteria instead of using echocardiography, it was evident that there were massive cost savings relative to echocardiography (R1500 x 1000) per 1000 positive patients (Table 7.1). Although adding eGFR and/ or CRP costs more than ECG alone, considerably more patients with LVH were detected (Table 7.1).

Table 7.1 Costs of doing the different analyses and the cumulative costs (per patient) of employing the various diagnostic methods alone and combined.

	LVH (%)	Cost per Patient	Patients detected/ 1000 positives	Additional patients detected/1000 positives	Cost saving*/ 1000 positives
Echocardiography	100	R1500.00	1 000	-	-
ECG	3	R 150.00	30	-	-
ECG + CRP	25.5	R 298.30	255	225	R270 382.50
ECG + eGFR	26.7	R 243.44	267	237	R297 909.00
ECG + CRP + eGFR	28.8	R 391.74	288	258	R285 931.08

* relative to echocardiography (Cost saving = cost of echocardiography minus the cost of ECG + CRP or eGFR or ECG + CRP + eGFR for additional patients detected/ 1000)

7.5 Conclusions

In conclusion, in the present thesis I provide substantial evidence to show that obesity markedly attenuates the relationships between currently recommended ECG criteria for LVH detection and LVMI; and that this translates in the obese into a negligible performance for Sokolow-Lyon and Cornell criteria and a low specificity for LVH detection using criteria that employ limb lead recordings only. I also show that eGFR and serum CRP concentrations are associated with LVMI independent of comorbidities and traditional risk factors as well as a number of non-traditional haemodynamic factors (eGFR), and thus may be employed to complement ECG criteria for LVH detection. Last, I show that eGFR and CRP concentrations do indeed enhance the specificity for LVH detection when employed together with ECG criteria that use limb-lead recordings only. Importantly, the overall sensitivity, specificity and performance of ECG criteria that use limb lead recordings only are compatible with that observed in lean and other population groups when eGFR and CRP are used to complement these criteria. Thus, in the present thesis I provide evidence to show that in groups of African ancestry obesity markedly diminishes the capacity to detect LVH using ECG criteria, but I also provide evidence for a potential solution to this conundrum.

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APPENDIX – Human Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Mr Fabian Maunganidze

CLEARANCE CERTIFICATE	**M10345**
PROJECT	The Impact of Obesity and Gender on Electrocardiographic Criteria for Left Ventricular Hypertrophy
INVESTIGATORS	Mr Fabian Maunganidze.
DEPARTMENT	School of Physiology
DATE CONSIDERED	26/03/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 29/03/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof A Woodiwiss

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...