Left ventricular geometry and function in Tanzanian patients with hypertension and diabetes

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Scientific environment

The present project was undertaken within the official institutional collaboration between Muhimbili University of Health and Allied Sciences (MUHAS) in Dar es Salaam, Tanzania and the University of Bergen in Norway aiming at faculty building at MUHAS. The project was performed within the Heart in Hypertension research group at the Institute of Medicine, University of Bergen. The Bergen Heart in Hypertension research group is chaired by professor Eva Gerdts and currently includes 1 professor, 1 professor emeritus, 3 post-doctoral fellows, 5 Ph.D. fellows and 2 research medical students. The research group has specialized in post-processing echocardiographic images by data programs in large clinical studies focusing on changes in myocardial structure and function in cardiovascular disease, in particular during chronic pressure overload. The research group has national collaborations with the University of Tromsø and the University of Oslo and a large international network with repeated exchange of junior and senior researchers creating a pulsating international environment. The main international partners are Weill Medical College, Cornell University, New York, USA (Professor Richard B. Devereux) and Federico II University, Napoli, Italy (Professor Giovanni de Simone).

The Echocardiography Research Laboratory at the Institute of Medicine, University of Bergen is DICOM based and fully digitalized with up-to-date equipment for analyses of all echocardiographic modalities including conventional echocardiography, deformation analysis by speckle tracking and three-dimensional echocardiography. Dedicated equipment for tissue Doppler analysis of myocardial mechanics is also available. The research group gives courses in echocardiography for medical students twice a year. The research fellows are included as teachers on these courses. An annual course for fellows under specialization in internal medicine or cardiology is also given. The latter is compulsory for obtaining board certification.

The Echocardiography Research Laboratory is well integrated within the Unit for Non-invasive Cardiac Imaging at Department of Heart Disease, Haukeland

University Hospital, providing an excellent basis for integrated training in clinical echocardiography and scientific utilization of echocardiographic images. The Echocardiographic research laboratory has served as a core laboratory in large multicenter studies involving thousands of patients.

The present project was initiated by the candidate, Pilly M. Chillo who had trained in echocardiography at the Department of Heart Disease at Haukeland University Hospital during specialization in cardiology. The project was funded by the Quota program through the Centre for International Health and by the Bergen Heart in Hypertension research group. All data collection took place at Muhimbili National Hospital in Dar es Salaam under supervision of co-mentor Dr. Johnson Lwakatare, Chief of Cardiology at the Department of Internal Medicine, MUHAS. All data analysis, the compulsory Ph.D. program and scientific writing took place at the University of Bergen, supervised by professor Eva Gerdts.

Acknowledgements

The present thesis is based on clinical studies carried out at the Muhimbili National Hospital in collaboration with Muhimbili University of Health and Allied Sciences in Dar es Salaam, Tanzania and the University of Bergen in Norway. All data was collected at the Department of Internal Medicine, Muhimbili National Hospital between May 2008 and November 2011.

First and foremost, I would like to express my sincere gratitude to Professor Eva Gerdts, my main supervisor and mentor for her guidance, enthusiastic encouragement and useful critiques for this research work. I am grateful for her academic teaching and for her valuable and constructive suggestions during the planning, implementation and completion of this research work. Her willingness to give her time so generously is very much appreciated. Without her, this work would not have been a success.

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I am grateful to my colleagues both at the Department of Heart Disease, Haukeland University Hospital and the Department of Internal Medicine, Muhimbili National Hospital. They all in one way or another supported me during the course of this work. My special thanks go to Åshild Rieck, Dana Cramariuc, Mai Tone Lønnebakken, Mohamed Janabi and Tatizo Waane for sharing with me their ideas as well as for their invaluable assistance.

I wish to thank other various individuals for their contribution to this project: Ms Tone Husebye for her support in echocardiographic data management while at the University of Bergen, Mr Chandru Punwani for being there at the very beginning of my echocardiography training, Mr Japhet Chiduo for his laboratory assistance, Sisters Sarah Isaac and Modesta Cyprian for their help in data collection and Dr Iramu Revilian, who was my research assistant.

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My heartfelt thanks go to my family, for their love, understanding and continuous support. Special thanks to my parents Mr and Mrs Chillo for making me the person I am today. To my brothers, sisters, cousins and everyone who wished me well, please receive my sincere thanks.

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List of abbreviations

A = Peak transmitral jet velocity during atrial contraction

E = Peak early transmitral jet

E' = Peak early mitral annular velocity

HbA_{1c} = Glycated haemoglobin

LAVI = Left Atrial Volume Index

LV = Left Ventricle/Ventricular

RWT = Relative Wall Thickness

UACR = Urine Albumin Creatinine Ratio

Abstract

From echocardiographic studies in hypertension, African Americans have been found to be more prone to develop cardiac target-organ damage than Caucasians. Hypertension is among the major upcoming health problems in Africa. However, there is a lack of knowledge about cardiac structural and functional changes in hypertension and diabetes in native sub-Saharan Africans.

This thesis consists of 3 studies that aimed at determining the prevalence, covariates and functional consequences of abnormal left ventricular (LV) geometry in native Tanzanian patients with hypertension and diabetes attending out-patient clinics at Muhimbili National Hospital in Dar es Salaam, Tanzania. In study I, 161 untreated hypertensive patients, and 80 age- and sex-matched normotensive controls were studied. Studies II and III included 123 type 2 and 61 type 1 diabetic patients with about 10 years duration of diabetes.

The prevalence of abnormal LV geometry was 77% in type 2 diabetic patients, 62.1% in untreated hypertensives, 40% in type 1 diabetic patients and 12.5% among the controls. Concentric LV hypertrophy was the most common abnormal LV geometric pattern in type 2 diabetes (in 47% of patients with abnormal LV geometry) and in untreated hypertensive patients (in 42% of patients with abnormal LV geometry), while concentric remodelling was the predominant type of abnormal LV geometry in type 1 diabetic patients (in 75% of patients with abnormal LV geometry) and in controls (90% of controls with abnormal LV geometry). Higher systolic blood pressure, obesity and impaired renal function were the main independent determinants of abnormal LV geometry both in patients with hypertension and in diabetes. Abnormal LV geometry was associated with subclinical LV myocardial systolic dysfunction both in hypertension and in diabetes, as well as subclinical LV diastolic dysfunction independent of clinical covariates.

A risk score comprising key clinical variables in standard assessment of diabetic patients (type of diabetes, hypertension, obesity and abnormal albuminuria) was

developed. This score demonstrated that presence of either hypertension, obesity or abnormal albuminuria in a patient with type 2 diabetes or presence of any 2 of these clinical variables in a type 1 diabetic patient identified 3 out of 4 diabetic patients with echocardiographic abnormal LV geometry (concentric remodelling or concentric LV hypertrophy, the main types of abnormal LV geometry in the diabetic patients).

The ability of enlarged left atrial volume index (LAVI) to detect subclinical LV diastolic dysfunction in diabetic patients was tested, and was found to be a good indicator of LV diastolic dysfunction in type 2 diabetic patients while LAVI reflected early diabetic cardiomyopathy in type 1 diabetic patients.

In conclusion, abnormal LV geometry is very prevalent in asymptomatic Tanzanian patients with hypertension and/or diabetes, increased by 4-6 folds compared to healthy controls, and is associated with subclinical LV systolic and diastolic dysfunction.

List of publications

1. Chillo P, Lwakatare J, Rieck A, Lutale J, Gerdts E. Prevalence and covariates of abnormal left ventricular geometry in untreated hypertensive patients in Tanzania. Submitted.

2. Chillo P, Lwakatare J, Lutale J, Gerdts E. Increased relative wall thickness is a marker of subclinical cardiac target-organ damage in African diabetic patients. *Cardiovascular J Afr* 2012; 23: online publication.

3. Chillo P, Rieck A, Lwakatare J, Lutale J, Gerdts E. Left atrial volume index as a marker of left ventricular diastolic dysfunction in asymptomatic Tanzanian diabetic patients. *Blood Pressure,* 2012; Early Online: 1–8.

Contents

1. INTRODUCTION

1.1 Hypertension and diabetes in a global health perspective

Hypertension and diabetes are major risk factors for cardiovascular disease, the leading cause of deaths worldwide.[1] In 2008, cardiovascular diseases alone were responsible for more than 17 million deaths globally.[1] Although the incidence of cardiovascular diseases has been declining in some high-income countries over the past two decades, it has increased at a fast rate in low- and middle-income countries.[1] The World Health Organization has ranked hypertension among the 3 top health problems in the world, including in Africa.[2]

The prevalence of hypertension is estimated to be 40% among adult general population globally, with the World Health Organization Africa region having the highest prevalence of around 46%.[3] In people with hypertension, the risk of cardiovascular diseases doubles for each incremental increase of 20/10 mmHg of blood pressure, starting as low as 115/75 mmHg.[4] In addition to causing coronary heart disease and cerebrovascular disease, hypertension, in particular if uncontrolled, is the main cause of heart failure in women and the second most frequent cause in men, as well as a major cause of renal failure, peripheral vascular disease, and damage to retinal blood vessels.[2]

The prevalence of diabetes was estimated to be 10% globally in 2008,[1] and while it was once considered rare in sub-Saharan Africa,[5, 6] type 2 diabetes has increased over the past 2 decades to the current prevalence approaching that in developed countries. Diabetes is associated with a 2-3 times increased risk for cardiovascular events, and cardiovascular diseases, including heart failure are responsible for about 60% of total mortality in diabetic patients.[1]

The rapid rise of hypertension, type 2 diabetes and other cardiovascular risk factors in sub-Saharan Africa over a fairly short period of time is attributable mainly to changes in lifestyle and dietary habits, which are a result of rapid urbanization and adaptation to western lifestyle.

1.2 Hypertension and abnormal LV geometry

Hypertension is a well-known cause of abnormal LV geometry, and three specific types of abnormal LV geometry have been described in hypertensive populations, based on combining LV mass indexed for body size and the ratio between wall thickness and internal LV chamber dimension (relative wall thickness [RWT]).[7] The different abnormal LV geometric types have been associated with specific clinical and hemodynamic factors as well as individual prognostic importance.[8, 9] Only about 6 to 20% of the variability of LV muscle mass is accounted for by blood pressure.[10] Other factors such as gender, race and high dietary sodium intake, presence of other comorbidities like obesity, renal insufficiency, metabolic syndrome, diabetes mellitus as well as genetics may contribute to the increase in LV mass in hypertension in individual patients beyond the effect of elevated blood pressure itself.[11-13]

In studies performed in the United States of America, race-associated differences in LV and left atrial adaptation to chronic hypertension have been described.[14-16] Particularly, LV mass, RWT and LV hypertrophy were higher among treated hypertensive African Americans compared to Caucasians participating in Hypertension Genetic Epidemiology Network study.[16] Moreover, in the Dallas Heart Study, African Americans had higher LV mass and a 2- to 3-fold higher prevalence of LV hypertrophy in the general population.[14] Finally, among hypertensive veterans, greater RWT (more concentric LV geometry) was reported in African American men compared to Caucasians.[15]

However, results from studies on African Americans with hypertension may not correctly reflect findings in native hypertensive Africans who have never emigrated, and therefore have been exposed to quite different lifestyle, socio-economical and

environmental factors. Only few studies on LV structure and function have so far been performed in native hypertensive Africans living in sub-Saharan Africa.[17-19] In particular, few data on untreated hypertensive patients have been published from the region, and only 1 previous study had included a healthy control group.[18] There is therefore a need for additional studies on cardiac target-organ damage in hypertensive Africans living in sub-Saharan Africa as basis for management and awareness of this emerging major health problem in the region.

1.3 Diabetes and abnormal LV geometry

The co-existence of type 2 diabetes with other cardiovascular risk factors such as hypertension and obesity may contribute to the association of diabetes with higher prevalence of abnormal LV geometry. In the Framingham study, primarily including Caucasians, a significant increase in LV wall thickness was particularly seen in women with diabetes[20] and type 2 diabetes was associated with higher LV mass and wall thicknesses in both men and women participating in the Strong Heart Study in North American Indians.[21] Furthermore, in a large multiracial study of hypertensive patients with LV hypertrophy, concomitant type 2 diabetes was associated with less reduction in LV hypertrophy and less improvement in LV systolic function despite aggressive systematic antihypertensive treatment, suggesting impaired cardiac benefit from blood pressure treatment when type 2 diabetes and hypertension coexist.[22] In patients with type 2 diabetes, insulin resistance and peripheral hyperinsulinemia is common, and most type 1 diabetic patients have peripheral hyperinsulinemia. Insulin is a known cardiovascular growth factor and insulin treatment has been associated with diabetes related hypertrophy in the arterial wall as well as LV hypertrophy.[23, 24]

In patients with type 1 diabetes, increase in LV mass and subclinical LV dysfunction have been associated with diabetic nephropathy, hypertension, high dietary sodium intake as well as the duration of diabetes.[25-27] Although atherosclerosis and hypertension may account for many of the myocardial abnormalities in patients with diabetes, a specific form of diabetic cardiomyopathy has also been described.[28-30]

Diabetic cardiomyopathy is a result from myocardial damage in diabetic patients caused by the metabolic changes from diabetes itself, including cardiomyocyte apoptosis, interstitial fibrosis and disturbances in cellular calcium homoeostasis.[31] This can echocardiographically be characterized by chamber dilatation and hypertrophy, as well as LV systolic and diastolic dysfunction [21, 32] and an important consequence of diabetic cardiomyopathy is heart failure.[33]

Independent of type of diabetes, there is lack of information about the prevalence, covariates and functional consequences of abnormal LV geometry in diabetic Africans living in sub-Saharan Africa.

1.4 Impact of abnormal LV geometry on LV function

Following the LaPlace's law, the LV adaptation to chronic pressure overload is an increase in wall thickness to reduce LV wall stress and maintain LV ejection fraction. However, LV adaptation to chronic pressure overload in individual hypertensive patients is influenced by comorbidities like diabetes, obesity, renal insufficiency and arterial changes as well as by gender, race and age, as depicted above.[11-13] Echocardiographic studies have demonstrated that although LV systolic chamber function measured by ejection fraction may be preserved in early stages of hypertension, LV systolic midwall function is often suppressed, particularly in patients with increased RWT.[34] Furthermore, LV systolic function varies between different types of abnormal LV geometry.[35, 36] This variation is not fully explained by gender differences or LV chamber size.[35, 37] Among asymptomatic patients with mild hypertension, a mild to moderately reduced LV ejection fraction is found in 10% and a severely reduced LV ejection fraction in 3%.[38] Among hypertensive patients with signs of LV hypertrophy on the electrocardiogram, around 14% will have reduced LV ejection fraction.[39]

Independent of presence of abnormal LV geometry, 30-50% of patients with mild hypertension and up to 90% of patients with severe hypertension have signs of diastolic dysfunction which can be detected by echocardiography.[38] With progressive

impairment of diastolic relaxation as part of the hypertensive heart disease, LV diastolic dysfunction progresses, resulting in increased LV filling pressures, with left atrial enlargement and diastolic heart failure, also called heart failure with preserved LV ejection fraction, the classical type of hypertensive heart failure. However, enlarged left atrium in hypertension does not solely reflect LV diastolic function, but is also influenced by a number of other modifiable as well as non-modifiable factors, including age, gender, blood pressure level, LV hypertrophy, obesity, mitral valve regurgitation and atrial fibrillation, as demonstrated in the multiracial Losartan Intervention For Endpoint reduction in hypertension echocardiography sub study.[40]

Left atrial enlargement may be an early sign of hypertensive heart disease, and independent of presence of LV hypertrophy, left atrial enlargement has been associated with increased incidence of cardiovascular events and higher all-cause mortality.[40-42] However, it has been demonstrated that African American hypertensives have smaller left atrial size than their Caucasian counterparts,[43] which has further been linked to the lower incidence of atrial fibrillation in African Americans.[44] However, only a few studies on covariates of left atrial size in native Africans have been published,[45] and so far the relation between LA size and LV diastolic dysfunction among native Africans has not yet been published.

2. AIM OF THE THESIS

2.1 General Aim:

The aim of this thesis was to determine the prevalence and functional consequences of subclinical abnormal LV geometry in Tanzanian out-patients with hypertension and diabetes referred to Muhimbili National Hospital.

2.2 Specific Aims:

1. To assess the prevalence and covariates of abnormal LV geometry in untreated Tanzanian patients with hypertension
2. To determine the prevalence and covariates of abnormal LV geometry in type 1 and type 2 diabetic patients
3. To determine the prevalence and covariates of enlarged left atrial volume index (LAVI) and its relation to LV diastolic dysfunction in asymptomatic type 1 and type 2 diabetic patients

3. METHODS

3.1 Patient populations

3.1.1 Study I

All never-treated hypertensive patients who were referred to the out-patient clinic at the Department of Medicine, Muhimbili National Hospital between September 2009 and May 2010 were evaluated for inclusion in this study. Patients were included if they were ≥18 years of age, had seated blood pressure ≥ 140/90mmHg on two different occasions and had never been treated for hypertension. Patients with concomitant cardiovascular disease (including diabetes mellitus and symptomatic rheumatic valvular heart disease), pregnancy induced hypertension, or symptomatic end stage renal disease were excluded. Of the 200 patients received during the study period, a total of 39 patients were excluded, 10 due to concomitant diabetes mellitus , 6 due to symptomatic end stage renal disease and 23 patients who did not show up for the echocardiogram, leaving 161 (80.5%) patients available for inclusion.

3.1.2 Studies II and III

In studies II and III, 184 diabetic patients (123 with type 2 diabetes and 61 with type 1 diabetes) were included. These patients were part of a prospectively planned follow-up examination of 244 diabetic patients who previously participated in a study to determine the prevalence of microalbuminuria in diabetic patients attending Muhimbili National Hospital in 2003-2004.[46] In 2008, all 184 patients (75% of the original cohort) who were still receiving care at the clinic were invited to participate, and all agreed to participate in the present follow-up examination with echocardiography. For study III, LA volume could not be measured in 4 patients due to poor apical image windows, leaving 180 patients for that analysis.

3.1.3 Healthy controls

To be able to relate findings in the hypertensive population to values found in normotensive Tanzanian population, a healthy control group was included in the project. Eighty normotensive healthy adults matched for age- and gender distribution with the hypertensive patients were recruited to serve as controls in study I. They were recruited from hospital employees, family members escorting patients as well as prospective kidney donors referred for routine echocardiography. Controls were required to have no known disease of any kind, not using any type of medication and have seated clinic blood pressure <140/90mmHg documented on 2 or more occasions.

3.2 Clinical assessment and Laboratory tests

Structured questionnaires were used to record the participants' socio-demographic characteristics, cardiovascular risk factors and use of medications (appendices A, B, and C). Height, weight, waist and hip circumference were measured. Body mass index was calculated from body weight in kilogram divided by height in metres^2 and obesity was considered present when body mass index was ≥ 30kg/m^2.[47] Waist circumference measured at the level of umbilicus was used as a measure of central adiposity.

A mercury sphygmomanometer was used to measure blood pressure. An appropriate cuff size was used for each patient and measurements were done in a quiet room, with the patient in the sitting position after a five minutes' rest. A set of three readings, five minutes apart were performed by an experienced study nurse. For analysis, the average of the last two readings was taken as the patient's clinic blood pressure. Patients were considered as having hypertension when the clinic blood pressure was ≥140 mmHg systolic and/or 90 mmHg diastolic.[48] Hypertension was defined as elevated clinic blood pressure or use of antihypertensive medications in studies II and III.

Blood samples were drawn in the morning after an overnight fast and analyzed for creatinine, lipid profile (total cholesterol, low density and high density lipoprotein cholesterol) and glucose. Blood was also analyzed for glycated haemoglobin (HbA_{1c}) in the diabetic patients. Biochemical tests were performed with the use of a chemistry analyser (Abbot Architect, Illinois, USA) at the Muhimbili National Hospital laboratory, while blood glucose and HbA_{1c} were analyzed at the clinic using a HemoCue AB glucose analyzer (Angelholm, Sweden) and a DCA 2000+ analyser (Bayer Inc., New York, USA), respectively. Estimated glomerular filtration rate was calculated using the Cockcroft-Gault equation and was considered low when it was <60ml/min/1.73m^2.[49]

A spot early morning urine sample was collected and analyzed for albuminuria using the same equipment used to measure HbA_{1c} (the DCA 2000+ analyzer). Microalbuminuria was defined as urine albumin to creatinine ratio (UACR) >30 mg/g and macroalbuminuria as UACR >300mg/g.[50] Abnormal albuminuria was defined as UACR>30 mg/g. UACR was not tested among the healthy controls due to limited funding of the project.

Metabolic syndrome was defined as the presence of any 3 of the following: elevated waist circumference (≥102/88cm in men/women), elevated triglycerides (≥1.7mmol/l), reduced high density lipoprotein cholesterol (<1.03/1.3mmol/l in men/women), elevated blood pressure (≥130mmHg of systolic or ≥85mmHg of diastolic blood pressure) or elevated fasting glucose (≥5.6mmol/l), according to the American Heart Association/National Heart, Lung and Blood Institute criteria.[51]

3.3 Echocardiography

3.3.1 Echocardiography study protocol

All echocardiograms were performed by the primary investigator (PC) after receiving special training in echocardiography at the Non-invasive Cardiac Imaging Unit at Department of Heart Disease, Haukeland University Hospital, Bergen, Norway. A

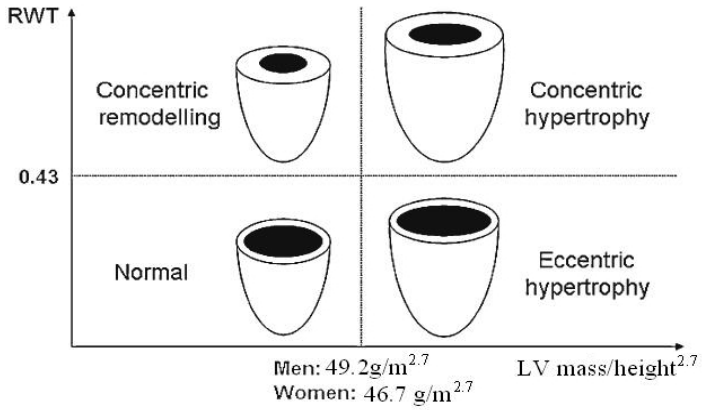
SONOS 7500 Phillips machine equipped with a 3-MHz transducer and second harmonic imaging was used. The standardized echocardiographic protocol used included two-dimensional parasternal long- and short-axis views as well as two-, three- and four-chamber images of the LV and left atrium. Pulsed-wave as well as colour Doppler studies of LV filling were recorded. Spectral tissue Doppler of the mitral annular plane movement was recorded in the apical four-chamber view.

All images were recorded on magnetic optical disks and on high resolution video tapes. Post processing of the digital images was done using a Tomtec (TomTec Imaging Systems GmbH, Unterschielssheim, Germany) work station equipped with Image Arena version 4.1 software. All image analysis was done at the Department of Heart Diseases, Haukeland University Hospital, in Bergen Norway. All studies were first read by the primary investigator and then proof read by the senior investigator, a highly experienced reader (EG).

3.3.2 Assessment of LV geometry

Quantitative echocardiography was performed following the American Society of Echocardiography guidelines.[52] LV mass was calculated using the anatomically validated formula by Devereux.[53] Due to the high prevalence of obesity among the study populations, LV hypertrophy was considered present when LV mass indexed for height$^{2.7}$ exceeded the prognostically validated cut-off values of 49.2g/m$^{2.7}$ in men and 46.7g/m$^{2.7}$ in women.[54, 55] RWT was calculated as the ratio of end-diastolic posterior wall thickness to end-diastolic LV internal radius and considered increased if ≥0.43. Categorization of patients into four LV geometric patterns was done based on LV hypertrophy and RWT measurements in combination.[52] Normal geometry was considered present if LV mass index and RWT were both normal, concentric remodelling was the combination of normal LV mass index and increased RWT, eccentric hypertrophy the combination of LV hypertrophy and normal RWT, and concentric hypertrophy was considered present if LV hypertrophy and increased RWT were both present (Fig. 1).

Fig. 1. Left ventricular geometric patterns



3.3.3 Assessment of LV systolic function

LV chamber systolic function was assessed by means of fractional shortening, stress-corrected fractional shortening, ejection fraction and stroke volume. Fractional shortening was calculated as (LV end-diastolic diameter – LV end-systolic diameter)/LV end-diastolic diameter. Stroke volume and ejection fraction were calculated using biplane Simpson's method and LV ejection fraction was considered low when <55%.[52]

LV myocardial systolic function was assessed from midwall fractional shortening, calculated using a previously validated equation, taking into consideration the epicardial migration of the midwall during systole, as well as from stress-corrected midwall shortening.[34] Circumferential end-systolic stress was estimated at the midwall using a cylindrical model.[56] Stress-corrected fractional shortening and stress-corrected midwall shortening were calculated as the ratio between the actual and predicted fractional shortening and midwall shortening for a given wall stress,

respectively.[34] Stress-corrected midwall shortening, a measure of myocardial contractility, was considered low if <87% in men and <90% in women.[57]

3.3.4 Assessment of LV diastolic function

Pulsed-wave Doppler was used for recordings of flow between the mitral leaflets tips in the apical four-chamber view and in the proximal LV outflow tract in the apical five-chamber view. The leading edge of the mitral flow pattern was traced to derive peak early (E) and atrial (A) velocities, the E/A ratio and E wave deceleration time. Isovolumic relaxation time was measured from the leading edge of the aortic valve closure spike to the leading edge of the mitral valve opening spike.

Early diastolic mitral annular plane velocity (E') was measured by spectral tissue Doppler from the medial annulus border in the apical four-chamber view. The ratio of the peak E velocity to medial mitral annulus velocity (E/E' ratio) was used as an estimation of LV filling pressure[58] and LV diastolic dysfunction was defined using the prognostically validated cut-off value E/E' ≥15.[59]

Left atrial volume was measured using biplane Simpson's method at the end of LV systole and indexed to body surface area to obtain left atrial volume index (LAVI). LAVI was considered enlarged if ≥29ml/m^2.[52] Assessment of mitral valve regurgitation was done using colour Doppler imaging and graded from 1 to 4 based on the neck width and length of the colour Doppler regurgitation.[60]

3.4 Statistical methods

Data management and statistical analysis was performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, Illinois, USA). Data are expressed as mean ± SD for continuous variables and as percentages for categorical variables. Groups of patients were compared using chi-square test for categorical variables and unpaired Student's t-test, one-way ANOVA with Sheffe's post hoc test or general linear model with Sidak's post hoc test for continuous variables, as appropriate. Bivariate

correlations were assessed by Pearson's correlation coefficient. Multivariate linear and logistic regression analyses were performed to determine independent predictors of higher LV mass index and RWT, as well as independent predictors of different measures of LV systolic and diastolic dysfunction. Receiver operating characteristic (ROC) curve analysis was used to obtain the optimal cut-off point for the prediction of increased RWT using the risk score formulated in study II. ROC analysis was also used to compare the relation of LV hypertrophy and LAVI with presence of diastolic dysfunction in study III, reporting area under the curve and 95% confidence intervals. Area under the curves were compared by DeLong's test[61] using MedCalc software version 12.1.3 (MedCalc, Mariakerke, Belgium). A two-tailed p-value of ≤ 0.05 was considered statistically significant.

3.5 Ethical considerations

The project was performed in accordance with the Helsinki declaration. Ethical approval for the studies was obtained from the Muhimbili University of Health and Allied Sciences' research and publication committee (Appendix D) and all participants signed a written informed consent form (Appendix E).

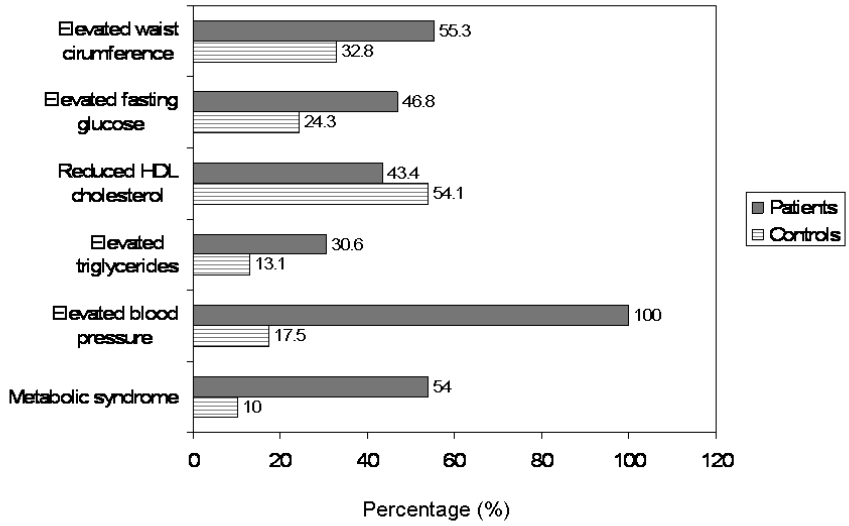
4. RESULTS

4.1 Study I

Prevalence and covariates of abnormal left ventricular geometry in untreated hypertensive patients in Tanzania

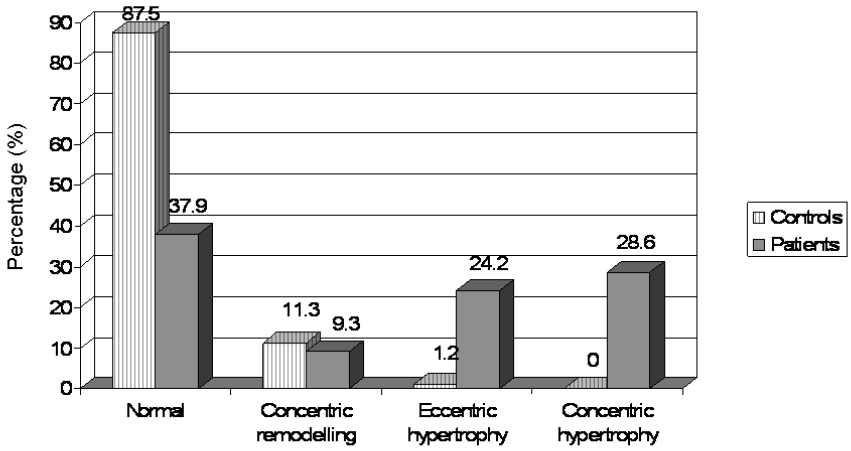
In this study, 161 untreated hypertensive adults (mean age 52.5 years, 60% women) and 80 healthy controls (mean age 46.6 years, 56% women) were studied. Hypertensive patients had mean blood pressure of 166/102±21/11mmHg while the mean blood pressure of the controls was 121/75±13/9 mmHg ($p<0.001$). Patients also had higher body mass index, waist circumference, heart rate, serum creatinine and lower creatinine clearance (all $p<0.05$). Obesity (body mass index $\geq 30 kg/m^2$) was present in 37% of patients and 20% of controls ($p<0.01$). Patients were more likely to have the individual components of the metabolic syndrome (Fig. 2). Fifty four percent of the patients and 10% of the controls met the criteria for the diagnosis of metabolic syndrome ($p<0.001$) (Fig. 2). In the total population, metabolic syndrome was more common in participants with abnormal LV geometry (52.7%) when compared to those with normal geometry (28.2%, $p<0.001$). When analyses were done separately for patients and controls, this difference was only seen among controls (prevalence of metabolic syndrome 40% in controls with abnormal LV geometry vs. 5.7% in controls with normal geometry, $p<0.01$) but not among patients (54.1% vs. 54.0%, respectively).

Fig. 2. Prevalence of metabolic syndrome and its individual components in patients and controls



In total, 62.1% of patients had abnormal LV geometry, predominantly LV hypertrophy. LV geometry differed significantly between patients and controls, $p<0.001$ between groups (Fig. 3). Among controls, abnormal LV geometry was found in 12.5% and in all, but 1 subject this was of the concentric remodelling type while eccentric LV hypertrophy was found in 1 (1.2%) control subject who was also obese.

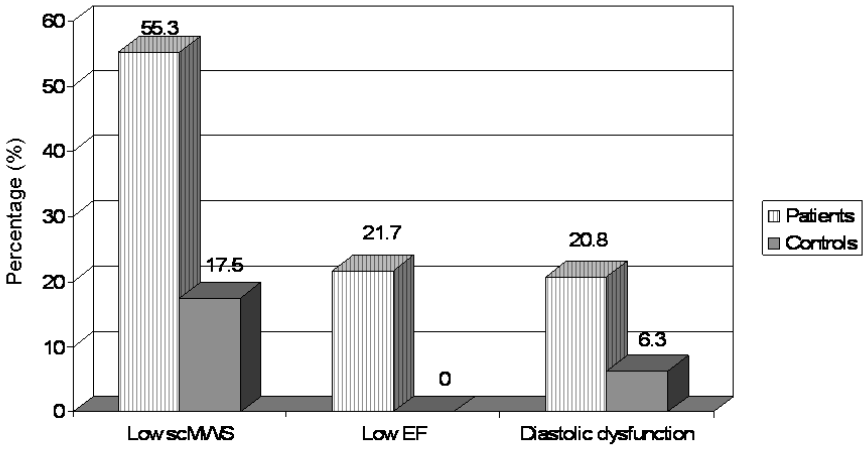
Fig. 3. Left ventricular geometric patterns in patients and controls



LV internal diameters as well as posterior-, septal-, and RWT were all significantly larger in patients (all $p<0.01$). Consequently, LV mass (192±74 vs. 121±32 g) and LV mass index (55.0±21.7 vs. 32.0±7.1 $g/m^{2.7}$) were both higher in patients when compared to controls, respectively (both $p<0.001$).

LV chamber systolic function measured as LV ejection fraction was lower in patients than in the controls (63% vs. 66%, $p<0.01$). LV myocardial contractility measured as stress corrected midwall shortening was also lower in patients than in controls (84% vs. 99%, $p<0.001$). The prevalences of impaired LV myocardial contractility (measured as low stress-corrected midwall shortening) and subnormal LV ejection fraction (<55%) were both higher in patients than in controls (Fig. 4).

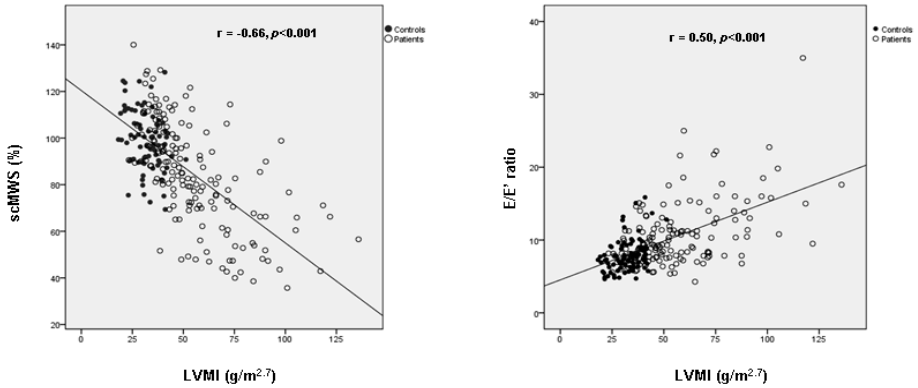
Fig. 4. Prevalence of low stress corrected midwall shortening (scMWS), low ejection fraction (EF), and LV diastolic dysfunction in patients and controls (p<0.01 for all).



The prevalence of low stress-corrected midwall shortening was higher in patients with abnormal LV geometry when compared to patients with normal LV geometry (80% vs. 14.8%, p<0.001). Similarly, among controls with abnormal LV geometry, low stress-corrected midwall shortening was present in 70%, but only in 10% of controls with normal LV geometry (p<0.001).

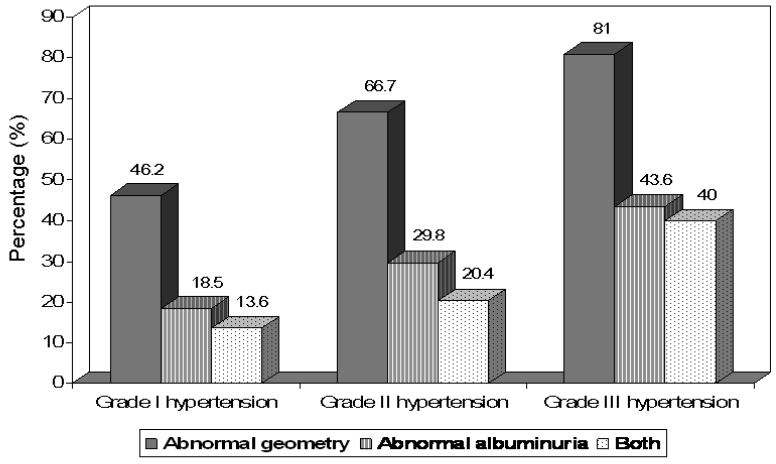
Patients had longer E wave deceleration time, isovolumic relaxation time and lower E/A ratio as well as lower early tissue Doppler velocity (E') and higher E/E' ratio (all p<0.001). LV diastolic dysfunction (measured as E/E' ratio ≥15) was 3.3 times more common in patients than in controls (Fig. 4). Among the 5 controls with LV diastolic dysfunction, all but 1 were obese women aged 60 years or above. Among patients, LV diastolic dysfunction was twice as common in those with abnormal LV geometry compared to those with normal LV geometry (26.7% vs. 11.7%, p<0.05). In the total population, higher LV mass index correlated with lower stress-corrected midwall shortening and higher E/E' ratio (Fig. 5).

Fig. 5. Correlation between LV mass index with stress corrected midwall shortening (scMWS) and E/E' ratio in the total population



In patients, abnormal albuminuria was present in 29.3%, and was more common in patients with abnormal LV geometry when compared to those with normal geometry (39.1% vs. 13.2%, p<0.01). Patients with impaired LV myocardial contractility were more likely to have combined abnormal LV geometry and abnormal albuminuria (35.9% vs. 8.6%, p<0.001), and the prevalence of both abnormal albuminuria and abnormal LV geometry increased with increasing severity of hypertension (Fig. 6).

Fig. 6. Prevalence of abnormal LV geometry, abnormal albuminuria and combined abnormal LV geometry and albuminuria in groups of patients with grade I, grade II and grade III hypertension. p=0.001, 0.03 and 0.008 for the differences in the prevalences of abnormal LV geometry, abnormal albuminuria and both, respectively.



In multivariate analysis involving the total population (multiple $R^2 = 0.60$, $p<0.001$), higher systolic blood pressure ($\beta = 0.28$, $p<0.001$), body mass index ($\beta = 0.20$, $p<0.01$), E/E' ratio ($\beta = 0.16$, $p<0.01$) and lower stress-corrected midwall shortening ($\beta= -0.44$, $p<0.001$) as well as estimated glomerular filtration rate ($\beta = -0.16$, $p<0.05$) were all independently associated with higher LV mass index. Similar findings were obtained when the analysis was performed in the patient group only. In addition, replacing estimated glomerular filtration rate with abnormal albuminuria in a second multivariate model including only the patients, revealed that abnormal albuminuria ($\beta = 0.17$, $p<0.01$) was independently associated with higher LV mass index. The independent covariates of higher RWT (i.e. concentric LV geometry) in the total population were higher systolic blood pressure ($\beta = 0.16$, $p<0.01$), E wave deceleration time ($\beta = 0.23$, $p<0.001$), and lower stress-corrected midwall shortening ($\beta = -0.66$, $p<0.01$) (multiple $R^2 = 0.55$, $p<0.001$). In an additional model, higher body mass index ($\beta = 0.14$, $p<0.05$) was independently associated with higher RWT

within the patient group. Neither age nor gender predicted abnormal LV geometry in this population.

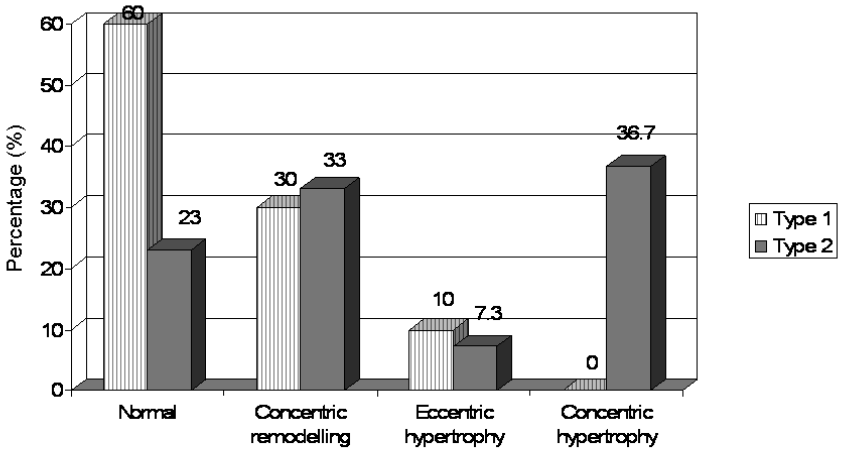
4.2 Study II

Increased relative wall thickness is a marker of subclinical cardiac target organ damage in African diabetic patients

In order to assess the prevalence of abnormal LV geometry among Tanzanian diabetic patients, 123 type 2 (mean age 55 years, 65% women) and 61 type 1 (mean age 22 years, 55% women) asymptomatic diabetic patients were studied. Type 2 diabetic patients had longer duration of diabetes (10.7 vs. 8.2 years) and included more hypertensive (82% vs. 18%) and obese (36.6% vs. 3.3%) patients (all $p<0.01$). Type 2 diabetic patients had larger LV dimensions, higher RWT, LV mass index as well as lower stress-corrected midwall shortening and impaired LV relaxation evidenced by lower E/A ratio, longer deceleration and isovolumic relaxation time (all $p<0.05$). In the total population low ejection fraction was present in 3.8%, and it was not statistically different between type 1 (1.6%) and type 2 (4.9%) diabetic patients, $p=0.280$. The prevalence of low stress-corrected midwall shortening was significantly higher in type 2 diabetic patients (74.8% vs. 39.3%, $p<0.001$). Patients with type 2 diabetes had higher E/E' ratio and were more likely to have LV diastolic dysfunction when compared to type 1 diabetic patients (20.5% vs. 3.5%), $p<0.01$.

LV geometry differed significantly among type 1 and type 2 diabetic patients (Fig. 7). The most common abnormal LV geometric pattern in type 2 diabetic patients was concentric LV hypertrophy, while concentric remodelling was the most common abnormal LV geometric pattern in type 1 diabetic patients (Fig. 7).

Fig. 7. Left ventricular geometric patterns in type 1 and type 2 diabetic patients



Overall, 58% of the total diabetic population had increased RWT, synonym with concentric LV geometry. The most important correlates of higher RWT were older age ($r = 0.36$ for type 1, $r = 0.20$ for type 2), higher systolic blood pressure ($r = 0.36$ for type 1, $r = 0.23$ for type 2) and more abnormal albuminuria ($r = 0.26$ for type 1, $r = 0.19$ for type 2), all $p<0.05$. In addition, lower estimated glomerular filtration rate ($r = -0.32$) and high density lipoprotein cholesterol ($r = -0.28$) significantly correlated with higher RWT among type 2 diabetic patients, but not in type 1. Having increased RWT was also associated with impaired systolic and diastolic LV function including lower myocardial contractility measured as stress-corrected midwall shortening, and delayed early LV diastolic relaxation measured as longer isovolumic relaxation time, longer deceleration time and reduced E/A ratio, both in type 1 and type 2 diabetic patients (all $p<0.05$). Multivariate linear regression analysis in the total population (multiple $R^2 = 0.69$, $p<0.001$) identified higher systolic blood pressure ($\beta = 0.30$), longer isovolumic relaxation time ($\beta = 0.17$), low stress-corrected midwall shortening ($\beta = 0.24$) as well as lower circumferential end-systolic stress ($\beta = -0.58$) as independent covariates of higher RWT (all $p<0.05$). These covariates remained

significant when separate analyses were performed in type 1 and type 2 diabetic patients, and in addition low estimated glomerular filtration rate ($\beta = 0.15$, $p<0.05$) was identified as an additional independent covariate of higher RWT in type 2 diabetic patients.

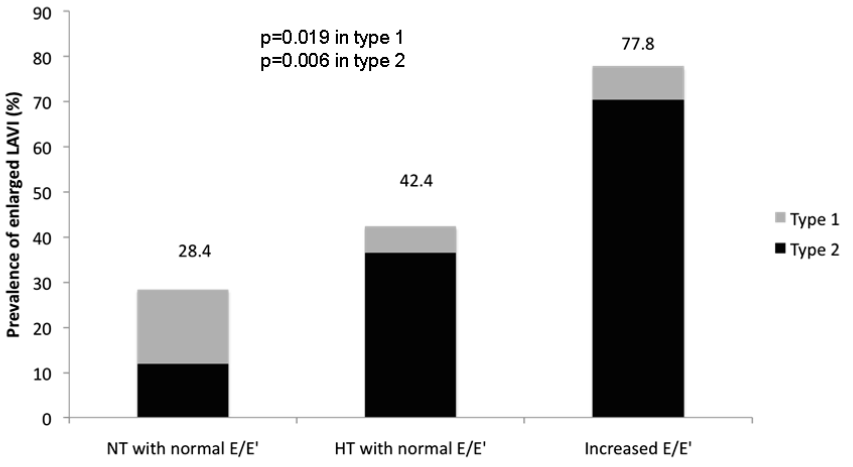
In binary logistic regression analysis, the independent covariates of increased RWT were found to be type 2 diabetes, presence of abnormal albuminuria, obesity and hypertension (all $p<0.05$). A risk score was calculated based on the beta coefficients in this model. This risk score had a positive predictive value of 76% (3 out of 4 patients) for identifying diabetic patients with abnormal LV geometry of either concentric remodelling or concentric LV hypertrophy type. Following this risk score, a patient with type 2 diabetes with any of the other three risk factors (obesity, hypertension or abnormal albuminuria), or a type 1 diabetic patient having any two of these additional cardiovascular risk factors would have a 76% chance of having cardiac target organ damage.

4.3 Study III

Left atrial volume index as a marker of left ventricular diastolic dysfunction in asymptomatic Tanzanian diabetic patients

To determine the prevalence of left atrial enlargement and its relation to LV diastolic dysfunction, 122 type 2 and 58 type 1 diabetic patients were studied. In the total population, enlarged LAVI was present in 38.3%. Enlarged LAVI was more common among type 2 diabetic patients (44.3% vs. 25.9%, $p<0.05$). Patients with enlarged LAVI were older when compared to patients with normal LAVI both in type 1 (26.9 vs. 18.7 years) and type 2 (56.8 vs 53.1 years) diabetic patients (both $p<0.05$). LV diastolic dysfunction (defined as E/E' ratio ≥ 15) was present in 15.1% of the total population and was more common in type 2 than in type 1 diabetic patients (20.5% vs. 3.5%, $p<0.01$). Diabetic patients with concomitant hypertension and those with increased E/E' ratio were more likely to have enlarged LAVI as well, especially among type 2 diabetic patients (Fig. 8).

Fig. 8. Prevalence of increased LAVI in different subgroups of patients: 1) Normotensive patients (NT) with normal E/E', 2) Hypertensive patients (HT) with normal E/E' and 3) Patients with increased E/E' according to type of diabetes.



In bivariate correlations, larger LAVI was significantly associated with higher systolic blood pressure, mean blood pressure, serum creatinine, LV mass index as well as higher E/E' ratio both in type 1 and type 2 diabetic patients (all $p<0.05$). In multivariate linear regression analyses, larger LAVI was independently associated with having LV diastolic dysfunction ($\beta = 0.20$), higher LV mass index ($\beta = 0.23$) and presence of mitral regurgitation ($\beta = 0.25$) in type 2 (all $p<0.05$), while larger LAVI was independently associated with higher LV mass index ($\beta = 0.30$), lower ejection fraction ($\beta = -0.37$) and longer duration of diabetes ($\beta = 0.27$) in type 1 diabetic patients (all $p<0.05$). In logistic regression analysis, enlarged LAVI was associated with a 3.3 times higher prevalence of LV diastolic dysfunction (95% confidence intervals 1.19 – 8.99, $p<0.05$) in the overall population independent of LV hypertrophy, type 2 diabetes and hypertension. Plotting the overall probability of this model with and without inclusion of LV hypertrophy among the covariates in a receiver operating characteristic curve demonstrated that the association between

larger LAVI and presence of LV diastolic dysfunction was independent of presence of LV hypertrophy.

5. DISCUSSION

5.1 Abnormal LV geometry in hypertension

LV hypertrophy is a common complication to chronic arterial hypertension, present in about 20 – 60% of uncomplicated hypertension and its prevalence increases with increasing grade of hypertension and presence of comorbidities, as also confirmed by the present studies in native sub-Saharan Africans. LV hypertrophy is a well-known marker of subclinical cardiovascular disease, often referred to as cardiac target organ damage, and is associated with 2-3 times increased cardiovascular morbidity and mortality, including stroke, myocardial infarction, heart failure, atrial fibrillation and sudden cardiac death.[62-67] Moreover, the type of LV geometric patterns adds prognostic information beyond that of LV mass or hypertrophy alone.[8, 9, 68, 69] The present thesis adds to current knowledge of cardiac target organ damage in native Africans with hypertension by demonstrating a high prevalence (62%) of abnormal LV geometry in asymptomatic, never-treated Tanzanian patients with hypertension referred for out-patient evaluation at Muhimbili National Hospital, in Dar es Salaam, Tanzania. The prevalence was 5 times higher than that found in the age- and gender-matched controls. Of note, LV hypertrophy was present in 52.8% of patients as opposed to 1.2% in controls.

The high prevalence of abnormal LV geometry found among never-treated Tanzanian hypertensive patients in the present project is in line with previous echocardiographic studies in hypertensive African Americans despite differences in lifestyle and comorbidities,[15, 16, 70] as well as previous studies in native Africans.[18, 19] Only a few echocardiographic studies have so far been published from hypertensive Africans living in sub-Saharan Africa. In a study of 100 untreated hypertensive Nigerians by Aje et al.,[18] abnormal LV geometry was found in 72%, while abnormal LV geometry was reported in 83% in a recent echocardiographic study of mostly treated hypertensive South African patients participating in the Baragwanath Hypertension

Study.[19] The differences in prevalence between the present and these previous African studies could be due to differences in level of blood pressure between the study participants but also presence of comorbidities. Although both the present study and that by Aje et al. excluded patients with comorbidities, more patients with subclinical renal impairment may have contributed to the higher prevalence of abnormal LV geometry seen in the study by Aje et al., but assessment of renal function was not included in their study.[18] On the other hand, the study by Libhaber et al. included patients who were previously treated hypertensives and therefore more likely to have longer duration of hypertension resulting in more target organ damage.[19] Worth a mention here though, is the finding of almost similar prevalences of abnormal LV geometry in the control groups in the present study and in the study by Aje et al.[18] In their study, the prevalence of concentric remodelling, eccentric hypertrophy and concentric hypertrophy among the controls was 11%, 3% and 0%, respectively while the corresponding prevalences were 11.3%, 1.2% and 0% in the present study. High prevalence of concentric remodelling has been reported also in normotensive African Americans participating in the Atherosclerotic Risk in Communities study.[71]

In bi- or multiracial echocardiographic studies performed in the United States of America, higher LV walls and mass have been found in African Americans when compared to Caucasians, both in hypertensive[15, 16] and in general population studies.[14, 72] The differences in LV mass and geometry between African Americans and Caucasians have been attributed to differences in lifestyle and socio-economical factors influencing comorbidities, treatment adherence and risk for renal or cardiovascular complications, but also race-associated increase in LV mass has been suggested.[73] In the Genetic Epidemiology Network of Arteriopathy Study that involved a cohort of hypertensive Caucasians and African American siblings, genetic variation that significantly influenced LV mass index as well as RWT was identified.[74] From this, the high prevalence of abnormal LV geometry also demonstrated in the present study among hypertensive patients in sub-Saharan Africa may be partly genetically explained. However, the prevalence of abnormal LV

geometry paralleled the severity of hypertension, increasing from 46% among patients with mild hypertension to 67% among those with moderate and 81% among those with severe hypertension, suggesting that independent of genetic impact on LV mass in Africans, presence and severity of a modifiable predictor like blood pressure has a substantial impact on the presence of cardiac target organ damage.

This study found that both impaired kidney function measured as low estimated glomerular filtration rate and abnormal albuminuria, indicating reduction in or damage to renal glomeruli, respectively, were independently associated with higher LV mass, in line with previous studies.[13, 75, 76] Of particular interest is the finding that abnormal albuminuria was independently associated with presence of LV hypertrophy independent of blood pressure, body mass index, age or gender. This is a clinically important finding, as a simple test of abnormal albuminuria could be used in identifying hypertensive patients at an increased risk of LV hypertrophy as well as identifying patients at increased risk of subsequent heart failure, as reported earlier.[77, 78] However, as demonstrated by our results, abnormal albuminuria was only present in 18.5 to 43.6% of patients depending on the severity of hypertension, and among patients with abnormal LV geometry, abnormal albuminuria was present in 39.1%. Thus, assessing albuminuria in a spot urine sample alone cannot substitute echocardiography in identification of cardiac target organ damage in native African patients with essential hypertension. Again, the study findings demonstrated that prevalence of abnormal albuminuria as a marker of renal hypertensive target organ damage increased in parallel with the severity of hypertension. Previous studies have demonstrated reduction in albuminuria and prevention of renal failure by antihypertensive treatment in hypertensive patients.[79, 80]

Contrasting findings in previous studies from the United States of America and Italy which showed that presence of the metabolic syndrome is strongly related to abnormal LV geometry in patients with hypertension,[11, 12, 81] the present study did not find a statistically significant association between presence of metabolic syndrome and abnormal LV geometry in the present study. Among hypertensive patients the

prevalence of metabolic syndrome was identical in those with and without abnormal LV geometry, suggesting that the presence of metabolic syndrome did not influence LV geometry in this study. However, the finding that higher body mass index was independently associated with both LV mass and RWT is in keeping with many previous studies both from hypertensive and general populations including African Americans as well as Caucasians.[11, 15, 70, 82, 83] These findings further emphasize the need to control overweight and obesity in patients with hypertension.

5.2 Abnormal LV geometry in diabetes

Previous publications from the Strong Heart Study in North American Indians have reported that LV mass and prevalence of LV hypertrophy are higher in diabetic subjects, in particularly if diabetes and hypertension co-exist.[84, 85] In the present studies 77% of type 2 and 40% of type 1 diabetic patients had abnormal LV geometry approximately 10 years after the diagnosis of diabetes. Concentric remodelling and concentric LV hypertrophy (i.e. concentric LV geometry) were the most common types of abnormal LV geometry. Only few echocardiographic studies have so far been performed in native sub-Saharan African type 2 diabetic patients while no study on type 1 diabetic patients has previously been reported from the region.[86] Therefore, the findings of these studies add to previous knowledge about subclinical diabetic heart disease in Africans in the sub-Saharan region.

The effect of diabetes, especially type 2 diabetes, on LV geometry has been well documented in North American Indians as well as in a population sample of hypertensive adults participating in the HyperGEN study.[84, 85] In these studies, type 2 diabetes alone was associated with higher LV mass and RWT compared to subjects without diabetes or hypertension and highest levels of LV mass and wall thicknesses were found when type 2 diabetes co-existed with hypertension, indicating that diabetes has an additive effect on LV mass and wall thickness on top of the effect of blood pressure. However, the prevalence of LV hypertrophy by echocardiography

was 38% among patients with combined type 2 diabetes and hypertension in both these studies,[84, 85] demonstrating a much higher prevalence of LV hypertrophy in the present study (44% combined eccentric and concentric LV hypertrophy) reflecting cardiac effects of diabetes in sub-Saharan Africans. Furthermore, in a recent echocardiographic study of normotensive type 2 diabetic Nigerians by Ojji et al., abnormal LV geometry was found in 51%[86] which is much lower than the 77% prevalence obtained in the mostly hypertensive type 2 diabetic patients participating in the current project.

The deleterious effect of hypertension on LV structure in diabetes is also demonstrated by the difference in LV geometry between type 2 and type 1 diabetic patients in the present project. Of note, hypertension was present in 82% in type 2 and 18% of the type 1 diabetic patients and systolic blood pressure was the main independent determinant of higher RWT in the total population and also within the type 1 and type 2 diabetic patient groups. However, patients with type 2 diabetes in this study were also older, had higher body mass index and longer duration of diabetes, all known factors that are associated with increase in LV mass in patients with diabetes.[84, 85] Our finding that concentric LV geometry was the predominant abnormal LV geometry is in agreement with findings from the HyperGEN study as well as the Strong Heart study, although these studies mostly included type 2 diabetic patients.[84, 85]

While the prevalence of hypertension was relatively low in the young type 1 diabetic patients in this cohort, prevalence of abnormal albuminuria was high, present in 40%. Renal impairment and abnormal albuminuria reflecting nephropathy in patients with diabetes are associated with cardiac target-organ damage as well as cardiovascular morbidity and mortality. In the present study, although including only asymptomatic patients without known cardiovascular disease or renal failure as assessed by estimated glomerular filtration rate, renal function was associated with concentric LV geometry only among type 2 diabetic patients. In contrast, within type 1 diabetic patients, no statistically significant association between lower kidney function and

higher RWT was found. Experimental studies have demonstrated that hyperglycemia promotes increased production of reactive oxygen species and collagen type 1 and II, promoting cardiomyocyte apoptosis as well as interstitial fibrosis.[31] Furthermore, changes in cellular calcium homoeostasis leading to both systolic and diastolic dysfunction have been described in experimental studies of diabetes in rodent models.[31] In particular altered expression, activity and function of key calcium transporters involved in excitation contraction coupling like SERCA (sarcoplasmatic endoplasmatic reticulum calcium ATPase), NCX (sarcolemma natrium-calcium exchange) and PMCA (plasma membrane calcium ATPase) have been demonstrated in these rodent studies.[31] From this, a disproportionate reduction in LV systolic function in relation to LV mass would be expected in diabetes. Indeed, this was reported in the echocardiographic substudy of the large Losartan Intervention For Endpoint reduction in hypertension study, as well as a reduced regression of LV hypertrophy and less improvement in LV systolic function following systematic antihypertensive treatment independent of type of drug.[22]

Diabetic patients with nephropathy have increased blood volume and body sodium and are often more likely to have hypertension and an exaggerated sympathetic nervous system as well as the rennin-angiotensin-aldosterone system, all factors that may explain the increase in LV mass associated with nephropathy.[87-89] In type 1 diabetes, nephropathy and duration of diabetes are causally associated with development of hypertension, while hypertension often precedes diagnosis of type 2 diabetes.[27, 87, 88, 90]

In the present project, we found body mass index to correlate with concentric LV geometry in the total diabetic population, but obesity did not predict presence of concentric LV geometry in multivariate analysis, contrasting other reports.[70, 83] However, our finding that obesity was associated with LV hypertrophy is in agreement with studies from others.[15, 71] Furthermore, both obesity and diabetes are associated with sympathetic activation, insulin resistance, hyperglycemia and

peripheral hyperinsulinemia which together with hypertension are among the main mechanisms inducing LV hypertrophy in such patients.[91]

5.3 Functional consequences of abnormal LV geometry

Independent of presence of abnormal LV geometry, 30-50% of patients with mild hypertension and up to 90% of patients with severe hypertension have signs of diastolic dysfunction which can be detected by echocardiography.[38] However, LV systolic function, whether measured as LV ejection fraction or as stress-corrected midwall shortening, is influenced by LV geometry in patients with hypertension as well as chronic pressure overload due to aortic valve stenosis.[35-37]

As demonstrated by the multivariate analysis in the present project, lower stress-corrected midwall shortening was particularly associated with increased RWT, independent of LV mass index, confirming findings in other studies that concentric LV geometry is especially associated with depressed myocardial contractility.[39] In a study of 960 hypertensive patients with electrocardiography LV hypertrophy by Wachtell et al., subnormal LV ejection fraction was present in 14% and low stress-corrected midwall shortening in 26%.[39] The prevalence of echocardiographic LV hypertrophy was 70% in that study which predominantly included Caucasians, the majority previously treated with antihypertensive drugs. While the prevalence of subnormal LV ejection fraction was lower in the study by Wachtell et al.,[39] the prevalence of depressed LV myocardial contractility was higher in the present study which demonstrated low LV ejection fraction in 21.7% and low stress-corrected midwall shortening in 55.3%, indicating an overall more depressed LV systolic function in our never-treated patients despite being on average 10 years younger, free of concomitant type 2 diabetes and despite having lower prevalence of abnormal LV geometry.

Both subnormal LV ejection fraction and stress-corrected midwall shortening predict incident heart failure as well as cardiovascular outcome independent of LV mass and clinical risk factors in large randomized trials as well as in prospective observational studies.[92, 93] Of interest though is the finding that LV midwall systolic performance significantly improved during effective antihypertensive treatment, following reduction in LV mass and hypertrophy in a study by Muiesan et al.[94] However, in hypertensive patients with concomitant type 2 diabetes, the cardiac benefit following systematic aggressive antihypertensive treatment was attenuated, including less reduction in LV mass and less improvement in systolic function even after 4-5 years of treatment.[22] Furthermore, in severely obese hypertensive patients, residual LV hypertrophy was present in 70% of treated hypertensive patients, explaining the high cardiovascular event rate in such patient, in particular hospitalization for heart failure and cardiovascular death.[95, 96]

Concentric LV geometry has been particularly associated with impaired LV relaxation and diastolic dysfunction. The finding that concentric LV geometry was independently associated with longer E wave deceleration time is in agreement with findings from the HyperGEN study which found that the odds of having abnormal LV relaxation were 2.3-fold greater when LV geometry was concentric.[97] In the present project, LV diastolic function was assessed by echocardiography using combination of LV filling pressure, early diastolic mitral annulus velocity and left atrial size. Several of these measures have prognostic value as demonstrated in previous publications, including mitral deceleration time index, E/A ratio, E/E' ratio and left atrial size.[98, 99] In patients with electrocardiographic LV hypertrophy, antihypertensive treatment resulted in significant improvement in transmitral flow patterns, and although this change was not associated with reduced cardiovascular morbidity and mortality, it was associated with reduced risk of hospitalization for heart failure.[100]

From the South African Heart of Soweto study it was previously reported that among Africans hospitalized with congestive heart failure hypertension, diabetes and obesity

were present in >80% of patients.[101] Furthermore, pure diastolic heart failure was found in 23%, and particularly associated with diabetes. The present studies add to this knowledge by a much more detailed assessment of LV structure and systolic and diastolic function in asymptomatic diabetic patients. In particular, diastolic dysfunction was found in 20.5% of type 2 diabetic patients in the present study, and associated with co-existing hypertension, while diastolic dysfunction was rare among type 1 diabetic patients.

5.4 Can abnormal LV geometry be predicted from clinical variables?

Presence of abnormal LV geometry signifies for the individual hypertensive patient a very high risk for cardiovascular events including heart failure, stroke, myocardial infarction and sudden cardiac death.[48] Particularly in hypertensive patients with moderately elevated blood pressure or few additional cardiovascular risk factors, identification of hypertensive target organ damage significantly changes the recommended management by the guidelines.[48] An important question is whether abnormal LV geometry in patients with hypertension and diabetes can be predicted from daily clinical variables in a setting like Tanzania where echocardiograph is not readily available. In patients with hypertension, use of single urine albumin test can identify patients at increased risk of LV hypertrophy as abnormal albuminuria was found to independently predict higher LV mass index in the hypertensive population. However, and as pointed out earlier, measurement of abnormal albuminuria cannot replace echocardiography as abnormal albuminuria was only present in 39.1% of patients with abnormal LV geometry. These findings are in line with previous findings in a large multiracial study of hypertensive patients with echocardiographically determined LV hypertrophy, reporting a prevalence of abnormal albuminuria of 33%.[75]

The level of blood pressure at presentation can however give a better indication of the presence of abnormal LV geometry. As demonstrated by our results, patients with stage II and III of hypertension were more likely to have abnormal LV geometry, and

among patients with severe hypertension, 81% had abnormal LV geometry on the echocardiogram.

As demonstrated, in patients with type 2 diabetes, presence of either of obesity, hypertension or albuminuria increased the chance that the patient will also have abnormal LV geometry to 76%, while for type 1 diabetic patients, presence of two of these factors indicated a 76% probability of having abnormal LV geometry.

6. Limitations

Some important study limitations should be mentioned. Although this project used more standardized and advanced echocardiography than previous publications on hypertensive and diabetic cardiac target organ damage on native sub-Saharan Africans, a limited number of patients and controls were studied. Further studies in more rural settings would add potential scientific and clinically important knowledge.

Furthermore, deformation analysis including strain and strain rate was not used, as this was not available on the provided echocardiograph at Muhimbili National Hospital. Adding deformation analysis is useful to detect subclinical LV dysfunction in patients despite normal LV ejection fraction.[102] However, beyond LV ejection fraction, we assessed midwall function with prognostically validated measures in hypertensive populations,[92] including midwall shortening and stress-corrected midwall shortening which hypothetically may be closely associated with global longitudinal strain.

Ambulatory blood pressure measurement was not available. White coat hypertension could therefore not be excluded from the hypertensive group. However, given the high prevalence of target organ damage, it is highly unlikely that white coat hypertension was prevalent among the patients. We can also not exclude that one or more control subjects may have been hypertensive despite normal office blood pressure on at least two visits, or that diabetic patients may have been misclassified. Such errors would lead to an underestimation of the true impact of hypertension on subclinical target-organ damage in native Africans.

Dietary salt intake is known to affect blood pressure as well as hypertensive cardiac and renal complications in particular in Africans.[103] Dietary salt intake can be measured in collected 24 hour urine samples or from standardized dietary questionnaires. The present project did not include measurement of daily salt intake

due to the complexity of these methods which were not available within the setting at the out-patient clinic.

7. Perspectives

The results of this thesis provide an insight to the burden of cardiac target-organ damage in native African patients with hypertension and diabetes attending care at a referral hospital. These results should be used as a tool in creating awareness, first at the institution level but also at the national level regarding the burden of hypertensive and diabetic heart disease in such patients. The results should together with WHO recognition of hypertension among the three most important health problems in Africa, inspire development of strategies for cardiovascular prevention in Tanzania. Although echocardiographic assessment of cardiac target organ damage is not feasible within such a strategy, measurement of blood pressure is. Indeed presence of concomitant hypertension in type 2 diabetes and presence of severe hypertension in non-diabetic hypertensive patients was the best predictor of presence of cardiac target organ damage in this project.

Future studies should focus on the pathophysiology of LV hypertrophy and abnormal LV geometry among native Africans and particularly focus on determining why such target-organ damage is very prevalent in native Africans. Long term follow up studies on patients with hypertension and diabetes are also recommended so as to confirm the prognostic importance of abnormal LV geometry demonstrated in previous studies in other races also in native African patients.

8. Conclusions

The aim of this thesis was to determine the prevalence and functional consequences of subclinical abnormal LV geometry in Tanzanian out-patients with hypertension and diabetes referred to Muhimbili National Hospital. The following conclusions were found for the pre-specified aims:

Study 1: To assess the prevalence and covariates of abnormal LV geometry in untreated Tanzanian patients with hypertension

The prevalence of abnormal LV geometry was 62.1% in untreated native Tanzanian patients with hypertension, 5 times higher than in age- and gender- matched normotensive controls. Higher systolic blood pressure, body mass index and presence of abnormal albuminuria were the main determinants of abnormal LV geometry. Presence of abnormal LV geometry was associated with subclinical LV systolic and diastolic dysfunction.

Study 2: To determine the prevalence and covariates of abnormal LV geometry in type 1 and type 2 diabetic patients

The prevalence of abnormal LV geometry was 77% in type 2 and 40% in type 1 diabetic patients attending care at Muhimbili diabetic out-patient clinic. Concomitant hypertension and higher systolic blood pressure greatly influenced the presence of abnormal LV geometry both in type 1 and type 2 diabetic patients, and in the total population obesity and abnormal albuminuria were particularly associated with LV hypertrophy. Presence of abnormal LV geometry was associated with subclinical LV systolic and diastolic dysfunction.

Study 3: To determine the prevalence and covariates of enlarged left atrial volume index (LAVI) and its relation to LV diastolic dysfunction in asymptomatic type 1 and type 2 diabetic patients

The prevalence of enlarged LAVI was 44.3% in type 2 and 25.9% in type 1 asymptomatic diabetic patients attending care at Muhimbili diabetic out-patient

clinic. In type 2 diabetic patients, enlarged LAVI independently predicted presence of LV diastolic dysfunction, while in type 1 diabetic patients, enlarged LAVI was associated with lower systolic function and longer duration of diabetes, but not with presence of LV diastolic dysfunction.

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