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The transition from obesity-induced left ventricular hypertrophy to abnormalities of cardiac function

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THE TRANSITION FROM OBESITY-INDUCED LEFT VENTRICULAR HYPERTROPHY TO ABNORMALITIES OF CARDIAC FUNCTION

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ABSTRACT

There is considerable evidence to show that obesity is associated with the development of heart failure independent of traditional risk factors. However, clarity is required on the process involved in the transition from obesity-associated left ventricular hypertrophy (LVH) to LV dysfunction. In the present thesis I evaluated the extent to which central obesity explains variations in LV diastolic function at a community level independent of LV mass (LVM), LV remodelling or haemodynamic factors; whether obesity-related increases in LVM exceeding that predicted by workload (inappropriate LVM [LVM_{inappr}] or alternative haemodynamic factors explains variations in LV ejection fraction (EF) at a community level; whether regression of LVM_{inappr} is more closely associated with improvements in EF than LVM or LVM index (LVMI); and whether obesity-associated insulin resistance may explain decreases in LV diastolic function and variations in LVM_{inappr}. Data were obtained in either 626 or 478 participants whom were representative of a randomly selected community sample and in 168 mild to moderate hypertensives treated for 4 months.

In 626 randomly selected participants over 16 years of age from a community sample with a high prevalence of excess adiposity (~24% overweight and ~43% obese) after adjustments for a number of confounders including age, sex, pulse rate, conventional diastolic (or systolic) blood pressure (BP), antihypertensive treatment, LVMI and the presence of diabetes mellitus or an HbA1c>6.1%; waist circumference ($p=0.0012$) was independently and inversely associated with a reduced early-ro-late transmitral velocity (E/A), with similar findings noted for e'/a' in a subset of 212 participants with tissue Doppler measurements. Waist circumference-E/A relationships persisted even after adjustments for other adiposity indices including body mass index (BMI) ($p<0.05$-0.005). No independent relationships between adiposity indices and E/e' were noted (n=212). In contrast to the effects on diastolic function, waist circumference

was not correlated with EF (p=0.83). The independent relationship between waist circumference and E/A was second only to age and similar to BP in the magnitude of the independent effect on E/A. The inclusion of relative wall thickness rather than LVMI in the regression equation produced similar outcomes. The inclusion of carotid-femoral pulse wave velocity (PWV), or 24-hour BP as confounders, failed to modify the relationship between waist circumference and E/A. Thus, waist circumference is second only to age in the impact of the independent association with E/A in a community sample with a high prevalence of excess adiposity. This effect was not accounted for by left ventricular hypertrophy or remodelling, 24-hour BP or arterial stiffness.

In 478 randomly selected participants from a community sample, waist circumference, but not BMI was independently associated with the homeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR was inversely correlated with E/A ($p<0.0001$) and in a multivariate model with adjustments for waist circumference, age, sex, conventional diastolic or systolic BP, diabetes mellitus or an HbA1c>6.1%, regular tobacco use, regular alcohol intake, pulse rate, treatment for hypertension and either LVMI or LV relative wall thickness in the model, the relationship betwreen HOMA-IR and E/A persisted (partial r=-0.13 to 0.14, $p<0.005$). With further adjustments for either 24-hour systolic or diastolic BP (partial r=-0.11, $p<0.05$, n=351) or for aortic PWV (partial r=-0.11, $p<0.02$, n=410), the independent relationship between HOMA-IR and E/A also remained. Therefore, the relationship between indices of an excess adiposity and abnormalities in LV diastolic function may be explained in-part by insulin resistance beyond haemodynamic factors.

In 626 randomly selected adult participants from a community sample with a high prevalence of obesity, the strongest independent predictor of LVM_{inappr} was BMI ($p<0.0001$). With adjustments for LV stress and other confounders there was a strong inverse relationship between LVM_{inappr} and EF (partial r=-0.41, $p<0.0001$), whilst only

modest inverse relations between LVM or LVMI and EF were noted (partial r=-0.07 to -0.09, p<0.05-0.09)(p<0.0001, comparison of partial r values). The independent relationship between LVM_{inappr} and EF persisted with further adjustments for LVM or LVMI (partial r=-0.52, p<0.0001). LVM_{inappr} and LV midwall fractional shortening were similarly inversely related (p<0.0001) and these relations were also stronger than and independent of LVM or LVMI. In conclusion, in a community sample with a high prevalence of obesity, inappropriate LVM is strongly and inversely related to variations in EF independent of and more closely than LVM or LVMI and BMI was the strongest independent determinant of inappropriate LVH. Therefore LVH is a compensatory response to workload, but when exceeding that predicted by workload, as may occur in obesity, is associated with LV systolic chamber decompensation.

In 168 mild-to-moderate hypertensives treated for 4 months, although in patients with an LVMI>51g/$m^{2.7}$ (n=112)(change in LVMI=-13.7±14.0 g/$m^{2.7}$, p<0.0001), but not in patients with an LVMI≤51g/$m^{2.7}$(n=56)(change in LVMI=1.3±9.3 g/$m^{2.7}$) LVMI decreased with treatment; treatment failed to increase EF in either group (1.2±10.8% and 2.7±10.7% respectively). In contrast, in patients with inappropriate LVH (LVM_{inappr}>150%, n=33) LVM_{inappr} decreased (-32±27%, p<0.0001) and EF increased (5.0±10.3%, p<0.0001) after treatment, whilst in patients with a LVM_{inappr}≤150% (n=135), neither LVM_{inappr} (-0.5±23%), nor EF (0.9±10.3%) changed with therapy. With adjustments for circumferential LV wall stress and other confounders, whilst on-treatment decreases in LVM or LVMI were weakly related to an attenuated EF (partial r=0.17, p<0.05), on-treatment decreases in LVM_{inappr} were strongly related to increases in EF even after further adjustments for LVM or LVMI (partial r=-0.63, confidence interval=-0.71 to -0.52, p<0.0001). In conclusion, decreases in LVM_{inappr} are strongly related to on-treatment increases in EF beyond changes in LVM and LVMI. LVH can therefore be viewed as a

compensatory change that preserves EF, but when in excess of that predicted by stroke work, as a pathophysiological process accounting for a reduced EF.

In 478 participants of a randomly selected community sample with adjustments for waist circumference, age, sex, conventional systolic BP, diabetes mellitus or an HbA1c>6.1%, regular tobacco use, regular alcohol intake, pulse rate, and treatment for hypertension, an independent relationship between HOMA-IR and LVM_{inappr} was noted (partial $r=0.14$, $p<0.002$). With further adjustments for either 24-hour systolic BP (partial $r=0.11$, $p<0.05$, $n=351$), aortic PWV (partial $r=0.13$, $p<0.02$, $n=410$), or circumferential LV wall stress (partial $r=0.12$, $p<0.02$, $n=478$) the independent relationship between HOMA-IR and LVM_{inappr} also remained. Thus, the relationship between indices of an excess adiposity and LVM beyond haemodynamic factors may be explained in-part by insulin resistance.

In conclusion, the results of the present thesis provide clarity on the process involved in the transition from obesity-associated LVH to LV dysfunction. In the present thesis I demonstrated that an index of central obesity explains a considerable proportion of the variation in LV diastolic function at a community level independent of LVM, LV remodelling and haemodynamic factors; that obesity-related increases in LVM exceeding that predicted by workload (LVM_{inappr}) or alternative haemodynamic factors explains a marked proportion of variations in EF at a community level; that regression of LVM_{inappr} is more closely associated with improvements in EF than LVM or LVM index (LVMI); and that obesity-associated insulin resistance may explain decreases in LV diastolic function and variations in LVM_{inappr} and hence EF. Therefore, studies are warranted to evaluate the impact of interventions that improve insulin sensitivity on obesity-related decreases in LV diastolic function and increases in LVM_{inappr}.

DECLARATION

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

…….

Carlos David Libhaber

…….day of …….., 20……

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: M940106 or M02-04-72 and renewed as M07-04-69 and M12-04-108.

…….

CARLOS DAVID LIBHABER

…….day of …….., 20……

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DEDICATION

This thesis is dedicated to my wife Elena, my children Ariel and Dana who are my constant inspiration and give me the will and courage to face new challenges, cross mountains and oceans (and even go to the gym), and my dear uncle Dr. Simon Vindver, whose wisdom and example guided me in medicine and in life.

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PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Publications

Libhaber CD, Norton GR, Majane OHI, Libhaber E, Essop MR, Brooksbank R, Maseko M, Woodiwiss AJ. Contribution of central and general adiposity to abnormal left ventricular diastolic function in a community sample with a high prevalence of obesity. Am J Cardiol 2009;104:1527-1533.

Woodiwiss AJ, Libhaber CD, Libhaber E, Sareli P, Norton GR. Relationship between on-treatment decreases of inappropriate versus absolute or indexed left ventricular mass and increases in ejection fraction in hypertension. Hypertension 2012;60(3):810-7.

Libhaber CD, Norton GT, Maseko MJ, Majane OH, Millen AM, Maunganidze F, Michel FS, Brooksbank R, Libhaber E, Sareli P, Woodiwiss AJ. Relationship between inappropriate left ventricular hypertrophy and ejection fraction independent of absolute or indexed mass in a community sample of black African ancestry. J Hypertens. 2013;31:169-76.

Presentations

Impact of Inappropriate Versus Absolute or Indexed Left Ventricular Mass on On-Treatment Changes and Community Variations in Ejection Fraction. Carlos D Libhaber, Angela J Woodiwiss, Muzi J Maseko, Olebogeng HI Majane, Aletta Esterhuyse, Elena

Libhaber, Pinhas Sareli, Mohamed R. Essop Gavin R Norton. South African Heart Association Congress, July 2012, Sun City, South Africa

Potential Mechanisms that Account for Obesity-Related Decreases in Left Ventricular Diastolic Function. Carlos Libhaber, Gavin R Norton, Olebogeng HI Majane, Muzi J Maseko, Pinhas Sareli, Angela J Woodiwiss. South African Heart Association Congress, July 2012, Sun City, South Africa

Potential Mechanisms that Account for Obesity-Related Decreases in Left Ventricular Diastolic Function. Carlos Libhaber, Gavin R Norton, Olebogeng HI Majane, Muzi J Maseko, Pinhas Sareli, Angela J Woodiwiss. South African Hypertension Society Meeting. March 2012, Cape Town, South Africa.

LIST OF ABBREVIATIONS

ACE: angiotensin-converting enzyme

ACE-I: angiotensin-converting enzyme inhibitor

ANOVA: analysis of variance

APOGH: African Study of Genes in Hypertension

ARB: Angiotensin receptor antagonists

ATP: Adenosine triphosphate

BMI: body mass index

BP: blood pressure

CHS: Cardiovascular Health Study

CI: confidence interval

DBP: diastolic blood pressure

DM: diabetes mellitus

E/A: early (E)-to-late (atrial)(A) transmitral flow velocity ratio

ed: end diastole

EF: ejection fraction

es: end systole

FS: fractional shortening

FSmid: midwall fractional shortening

GITS: gastrointestinal therapeutic system

$g/m^{2.7}$: $gram/meter^{2.7}$

H: wall thickness

HbA1c: glycosylated hemoglobin

HDL: high density lipids

HOMA-IR: homeostasis model assessment of insulin resistance

HOPE: Heart Outcomes Prevention Evaluation

HyperGen: Hypertension Genetic Epidemiology Network Study

IVS: inter-ventricular septal wall thickness

Kg/m^2: Kilogram/meter^2

LIFE: Losartan Intervention for Endpoint Reduction in Hypertension

LV: left ventricle

LVED: left ventricular end diastolic

LVEDD: left ventricular end diastolic diameter

LVEF: left ventricular ejection fraction

LVESD: left ventricular end systolic diameter

LVH: left ventricular hypertrophy

LVID: left ventricular internal diameter

LVM: left ventricular mass

LVM_HT: LV mass adjusted to height

LVM_{inappr}: Inappropriate left ventricular mass

LVMI: left ventricular mass index

MESA: The Multi-Ethnic Study of Atherosclerosis

NC: North Carolina

NCEP: Third report of the National Cholesterol Education Program

NHANES: National Health and Nutrition Examination Surveys

PWT: posterior wall thickness

PW: pulse wave

PWV: pulse wave velocity

RWT: relative wall thickness

SBP/DBP: systolic BP/diastolic BP

SBP: systolic blood pressure

SHR: Spontaneously hypertensive rats:

Skinf: mean skin-fold thickness

SOWETO: South Western township

SR: slow release

TG: triglycerides

USA: United States of America

WC: waist circumference

WHR: waist-to-hip ratio

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PREFACE

The impetus to perform the studies described in the present thesis was derived from the increasing prevalence of obesity noted in urban, developing communities of African ancestry; the knowledge that obesity translates into a risk for the development of heart failure independent of a number of traditional risk factors; but the lack of understanding of the exact mechanisms responsible for this effect. As obesity is often difficult to manage through weight loss programmes, a better understanding of the process responsible for the development of heart failure in obesity is necessary to develop appropriate management strategies for the obese. Importantly, it is well acknowledged that obesity is one of the major determinants of left ventricular hypertrophy and that left ventricular hypertrophy is a strong and independent risk factor for the development of heart failure. Whether left ventricular hypertrophy is an important pre-requisite for the progression from obesity to either diastolic or systolic dysfunction and consequently heart failure, is currently unknown. In this regard, preclinical evidence of either diastolic or systolic dysfunction has been demonstrated to be a strong risk factor for the development of heart failure.

In the present thesis I evaluated the extent to which obesity may account for left ventricular diastolic dysfunction at a community level, and whether this relationship is largely determined by left ventricular hypertrophy, structural remodelling of the left ventricle, or the coexistence of insulin resistance, a metabolic change often associated with obesity. Moreover, because current evidence for a relationship between left ventricular hypertrophy and systolic chamber dysfunction of the heart is conflicting, I further evaluated the notion that left ventricular hypertrophy in excess of that predicted by stroke work, may be the major component of cardiac hypertrophy that accounts for systolic chamber dysfunction. In this regard, at a community level I noted that obesity

and coexistent insulin resistance were the major factors responsible for variations in left ventricular hypertrophy in excess of that predicted from stroke work.

In the present thesis, in chapter 1 I have first reviewed the scientific literature that describes the relationships between either obesity or left ventricular hypertrophy and abnormalities of LV function or the development of heart faillure. This review is designed to lead the reader through a series of arguments that support the hypotheses tested in the present thesis. Chapters 2-6 consist of a series of semi-independent chapters, each divided into an “abstract”, “introduction”, “methods”, “results” and “discussion” sections, describing the studies performed in the present thesis, the data obtained, and the implications of these data. Although these chapters are best dealt with as separate entities, throughout these chapters I have underscored the progression of the arguments provided. Finally, in chapter 7 I provide a summary and concluding statement of the work described in the present thesis.

In support of this thesis I am either first or second author on three papers published to date with second authorship indicating an equal contribution to these papers as the first author. These papers have been published in the *American Journal of Cardiology* (Libhaber et al 2009), the *Journal of Hypertension* (Libhaber et al 2013) and the journal *Hypertension* (Woodiwiss, Libhaber et al 2012). In addition, further manuscripts are currently being prepared for submission to international journals for consideration of publication.