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# The hypertensive heart in groups of African ancestry in South Africa

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# The Hypertensive Heart in Groups of African Ancestry in South Africa

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy.

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**Abstract**

Hypertensive heart failure is a major cause of death and disability in Africa and the world today. Although much is known about the transition to heart failure in hypertension, there is uncertainty as to the dominant haemodynamic determinant of cardiac dysfunction across the adult lifespan. Furthermore, whether in volume-dependent hypertension, the foremost cause of hypertension in Africa, these effects can be adequately detected by the presence of left ventricular (LV) structural changes, is uncertain. In 605 to 709 participants from a community-based study in SOWETO, using central arterial pressure assessments and aortic velocity and diameter measured in the outflow tract (echocardiography); contemporary approaches to central arterial waveform construction and the assessment of LV cardiac systolic and diastolic function (tissue Doppler indexes), we therefore assessed the haemodynamic determinants and LV structural changes that account for LV dysfunction across the adult age range. We show that LV diastolic function linearly declines with age across the full adult lifespan starting from late teenage years and the principle factor accounting for these effects is a linear age-related increase in aortic reflected (backward) wave pressures. In contrast, neither systemic vascular resistance (SVR), that component of forward wave pressures determined by the product of aortic flow and characteristic impedance to flow (Zc)($P_{QxZc}$), or total arterial compliance determined age-related decreases in LV diastolic function independent of backward wave pressures. However, after 50 years of age, age-related increases in backward wave pressure were determined by $P_{QxZc}$. Importantly, backward wave pressure effects were not adequately detected by brachial blood pressure (BP) measurements and hence alternative approaches to recognising the adverse effects are therefore required.

As the detection of LV structural remodelling is a well-recognised method of identifying the adverse cardiac effects of hypertension, we then assessed whether LV hypertrophy (LVH) or geometric remodelling accounted for the impact of backward wave pressures and BP on LV diastolic function. However, because LVH depends as much on increases in stroke work (SW) as on afterload, the dominant volume-dependence of

hypertension in this community sample (which increases stroke volume as hence SW), rendered LVH a poor index of the adverse effects of backward wave pressures and BP on LV diastolic function. This was explained by the lack of impact of SW on LV diastolic function. In addition, concentric LVH was as dependent on volume-dependent increases in stroke volume as eccentric LVH, and LV geometric remodelling was not associated with backward wave pressures or BP. Thus, concentric as opposed to eccentric LVH failed to better identify the presence of LV diastolic dysfunction.

The results of these studies either published, or in-press in the high impact journals, *Hypertension*, *Journal of Hypertension* and the *American Journal of Hypertension*, therefore provide insights into how best to prevent the development of hypertensive heart failure in Africa. In this regard, from 50 years of age, when brachial pulse pressure begins to increase, intense BP reduction is required in those with hypertension. This, is the only approach that will eliminate increases in backward wave pressures and hence prevent further deterioration of LV diastolic function. This is an essential approach as the impact of backward wave pressures is poorly detected at the brachial pulse; is not adequately indexed by the presence of concentric LV hypertrophy; and only a half of LV diastolic functional reserve remains at 50 years of age.

**Declaration**

I declare that this is my own unaided work; it is being submitted for the degree of Doctor of Philosophy in the Faculty of Health Sciences, 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.

Hamza Bello

Signed on 16th day of March, 2022 in Parktown

I certify that all studies contained in this thesis have the approval of the Committee for Research on Human Studies of the University of the Witwatersrand. The clearance numbers are M191086, M170401, M020472, M070469 and M1204108.

Professor Angela J Woodiwiss (supervisor1)

Professor Gavin R Norton (Supervisor 2)

Dr Vernice Peterson (Supervisor 3)

**Dedication**

This thesis is dedicated to patients with cardiovascular disease and the education of healthcare providers.

**Publications**

In support of the present thesis, the work included has resulted in the following publications in international journals.

1. Bello, H, Norton, G.R, Peterson,V.R, Mmopi, K. N, Mthembu, N, Libhaber, C. D, Masiu, M, Da Silva Fernandes, D, Bamaiyi, A. J, Peters, F, Sareli P. & Woodiwiss A.J. 2020. Hemodynamic Determinants of Age Versus Left Ventricular Diastolic Function Relations Across the Full Adult Age Range. *Hypertension,* 75**,** 1574-1583.
2. Bello H, Woodiwiss AJ, Naran R, Peterson VR, Libhaber CD, Mmopi KN, Mthembu N, Masiu M, Fernandes DD, Bamaiyi AJ, Peters F, Sareli P, Norton GR. 2021. Impact of Stroke Work on the Ability of Left Ventricular Mass to Account for Pressure Effects on Function in a Community with Prevalent Volume-Dependent Hypertension*. Journal of Hypertension,* 39 (10), pp.2092-2102.
3. Bello H, Norton GR, Peterson VR, Libhaber CD, Mmopi, Mthembu N, Masiu M, Daniel Fernandes DD, Bamaiyi AJ, Peters F, Sareli P, Woodiwiss AJ. 2021. Hemodynamic and Functional Correlates of Concentric versus Eccentric Left Ventricular Hypertrophy in a Community-Based Sample with Prevalent Volume-Dependent Hypertension. *American Journal of Hypertension*, 75, 1574-1583.

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**List of Abbreviations**

| | |
|---|---|
| α | Alpha |
| a’ | Peak velocity during late (atrial) diastole |
| A wave | Trans-mitral blood flow velocity in the late (atrial-A) period of left ventricular diastolic filling |
| ACE | Angiotensin-converting enzyme |
| Adj | Adjustment |
| AJW | Angela Jill Woodiwiss |
| ANOVA | Analysis of variance |
| ARBs | Angiotensin Receptor Blockers |
| ASCOT | Anglo-Scandinavian cardiac outcome trial |
| ASE | American society of echocardiography |
| ATP | Adenosine triphosphate |
| ALLHAT | Antihypertensive and lipid-lowering treatment to prevent heart attack trial |
| β | Beta |
| β-AR | Beta adrenergic receptor |
| BMI | Body mass index |
| B-mode | Bright mode |
| BP | Blood pressure |
| BSA | Body surface area |
| CDL | Carlos David Libhaber |
| CI | Confidence interval |
| Cm | Centimeters |
| cm/s | Centimeters per second |
| DBP | Diastolic blood pressure |
| DD | Diastolic dysfunction |
| DM | Diabetes mellitus |

| | |
|---|---|
| e’ | Peak velocity during early diastole at the mitral annulus |
| E/A | Ratio of E wave to A wave velocity |
| E/e’ | Index of Left Ventricular filling pressures |
| EAE | European association of echocardiography |
| ECG | Electrocardiogram |
| EDV | End diastolic volume |
| ED | End diastole |
| EDP | End diastolic pressure |
| EF | Ejection fraction |
| E wave | Trans-mitral blood flow velocity in the early period of left ventricular diastolic filling |
| F | Send endocardial fractional shortening |
| FSmid | Midwall fractional shortening |
| g | Gram |
| g/m | Gram per meter |
| HbA1c | Percentage glycated haemoglobin |
| HFpEF | Heart failure with preserved ejection fraction |
| HFrEF | Heart failure with reduced ejection fraction |
| HT | Hypertension |
| HYVET | Hypertension in the Very Elderly Trial |
| ISO | Isoproterenol |
| J Hypertens | Journal of hypertension |
| Kg | Kilogram |
| $Kg/m^2$ | Kg per $meter^2$ |
| LA | Left atrial |
| $LVM_{inappr}$ | Inappropriate Left Ventricular Mass |
| LAV | Left atrial volume |
| LV | Left ventricular |

| | |
|---|---|
| LV DD | Left ventricular diastolic dysfunction |
| LVEDD | Left ventricular end diastolic diameter |
| LVESD | Left ventricular end systolic diameter |
| LVH | Left ventricular hypertrophy |
| LVM | Left ventricular mass |
| LVMI | Left ventricular mass indexed for height$^{2.7}$ |
| LVMI-ht | Left ventricular mass indexed to height |
| LVMI-BSA | Left ventricular mass indexed to body mass area |
| MAP | Mean arterial pressure |
| Mm | Millimeters |
| MmHg | Millimeter of mercury |
| ml/m$^2$ | Millimeter per meter square |
| Ml/min | Millimeter per minute |
| µU/ml | Micro unit per millilitres |
| mmol/L | Micromole per liter |
| MRC | Medical research council |
| n | Number |
| NT | Normotensive |
| OR | Odd ratio |
| P | P-value or statistical significance |
| Pb | Wave Reflection Pressure/ Backward Wave Pressure |
| Pf | Forward Wave Pressure |
| Pi | Incident Wave/ Inflection Point |
| PP | Pulse pressure |
| PWED | Left ventricular posterior wall thickness at end diastole |
| PWES | Left ventricular posterior wall thickness at end systole |
| $P_{QxZc}$ | Peak Product of Flow and Characteristic Impedance |
| Q | Aortic Flow |

| | |
|---|---|
| RV | Right ventricle |
| $r^2$ | Goodness of fit |
| r | Correlation coefficient |
| RWT | Relative wall thickness |
| SAS | Statistical analysis system |
| SEM | Standard error of mean |
| SD | Standard deviation |
| SBPc | Central systolic blood pressure |
| SBP | Systolic Blood pressure |
| $sec^{-1}$ | Per second |
| SHEP | Systolic Hypertension in the Elderly Program |
| SOWETO | South west township |
| SHR | Spontaneously hypertensive rat |
| SVR | Systemic Vascular resistance |
| SW | Stroke work |
| TAC | Total Arterial Compliance |
| TDI | Tissue doppler imaging |
| USA | United States of America |
| Vs | Versus |
| WC | Waist circumference |
| WKY | Wistar Kyoto |
| Zc | Characteristic Impedance |

## List of Symbols

| | |
|---|---|
| > | greater than |
| < | less than |
| ≥ | greater than or equal to |
| % | Percentage |

**Preface**

With the increase in average age of populations worldwide, there has been a epidemiological transition which has shifted the burden of healthcare problems from communicable to non-communicable diseases. In this regard, cardiovascular disease is the major non-communicable disease responsible for death and disability in the world today. Although major advances in the management of coronary artery disease and stroke have been made over the past few decades, presently heart failure, from the time of diagnosis carries a very poor prognosis. Hypertension is a well-recognised cause of heart failure. Although a lack of detection of hypertension and poor blood pressure (BP) control when treated are major causes of hypertensive heart failure, there are several additional factors that may explain the transition to heart failure in hypertension. In the present thesis I assessed, across the adult lifespan, the haemodynamic determinants and role of structural remodelling of the left ventricle (LV) as factors that explain the transition to LV dysfunction in a community of African ancestry. In this regard, there were several reasons why these questions are important?

As will be highlighted in the introductory chapter to this thesis, the adverse cardiac effects of afterload on the heart may be mediated by a component of central arterial pressure that largely increases late systolic load and which is not detected at the brachial pulse. This would render the utility of brachial BP measurements of limited value for identifying and managing hypertension in a manner which prevents the transition to heart failure. However, until the time of the present thesis, the exact haemodynamic changes across the full adult lifespan, responsible for dysfunction of the heart in hypertension had not been identified. Given that brachial BP may be a poor index of the effects of afterload on the heart in hypertension, measurements of cardiac mass or geometry may be an important ancillary measure to index cardiac dysfunction. However, in groups of African ancestry we have recently demonstrated that volume-dependent increases in systemic flow are major determinants of hypertension. As systemic flow causes cardiac hypertrophy and influences geometric remodelling independent of BP, in the present thesis I therefore questioned the

utility of structural cardiac changes as adequate indices of afterload-induced effects on cardiac dysfunction in Africa.

The present thesis comprises of a series of semi-independent data chapters (chapters 2 to 4), each having its own introduction, methods, results and discussion sections. In the introduction to this thesis (chapter 1) we critically review the available evidence on the haemodynamic determinants of hypertension in groups of African origins and the possible role of structural cardiac remodelling as an index of cardiac dysfunction in hypertension in Africa. In this chapter we therefore argue in favour of conducting the studies that have been included in this present thesis. The conclusions chapter of the thesis (chapter 5) consolidates the findings of the data presented, underscoring the novelty of and giving perspective to these findings based on what is presently known and understood in the field. In support of the present thesis, the data presented in chapter 2 have been published in the journal *Hypertension* (Bello et al., 2020); the data presented in chapter 3 are presently in-press in the *Journal of Hypertension* (Bello et al., 2021a); and the data presented in chapter 4 are similarly currently in-press in the *American Journal of Hypertension* (Bello et al., 2021b).

# Chapter 1

## Haemodynamic Determinants and Structural Cardiac Changes in the Progression from Hypertensive Hypertrophy to Heart Failure.

## 1.0 Introduction

While over the past several decades significant advances have been made in the prevention and management of a number of cardiovascular events, including stroke, myocardial infarction, and critical limb ischaemia, heart failure persists as a major liability to healthcare systems and society (Borlaug and Redfield 2011, Buonacera et al 2018). Heart failure is a condition that results in survival rates similar to those of the worst possible malignancies (Cowie et al 2000, Stewart et al 2001). Thus, there is a need to better understand the pathophysiological basis of heart failure in order to identify novel preventative and therapeutic approaches. As will be discussed in the present chapter, there is substantial evidence to support a role for hypertension as a dominant risk factor for heart failure. In addition, the pathophysiological mechanisms responsible for the impact of hypertension on the heart have been well described. However, as will also be highlighted, hypertension still remains one of the major causes of heart failure in both economically developed and underdeveloped countries. Furthermore, as will also be argued in the present chapter, there are several outstanding issues related to the pathophysiological mechanisms responsible for cardiac dysfunction and hence the approach to risk detection in hypertensives who may ultimately progress to heart failure.

## 1.1 Hypertension as a cause of heart failure

There is substantial evidence to support a role for hypertension as a major cause of heart failure. In a meta-analysis of 23 landmark clinical trials of blood pressure (BP)-lowering in hypertensives, 29% of patients developed heart failure (Tocci et al 2008). This is a considerably greater incidence than one would expect in the general population. In a community sample of 5,143 participants from the Framingham Heart Study, during 20 years of follow-up (mean 14.1 years), hypertension antedated the development of heart failure in 91% of newly diagnosed patients (Levy et al 1996). With adjustments for confounders, the risk for developing heart failure in hypertensive compared with normotensives in the Framingham Heart Study was 2 to 3 times higher in men and women respectively (Levy et al 1996). In that study (Levy et al 1996), hypertension had the highest population-attributable

risk for heart failure, explaining 39% of cases in men and 59% in women. Importantly, at 80 years of age, the lifetime risk of heart failure was about 20% in the Framingham Heart Study, and this risk doubled for patients with a BP of 160/100 mm Hg compared with those with a BP of 140/90 mm Hg (Lloyd-Jones et al 2002). The risk for the development of heart failure in older hypertensives is reported to be attributed to an increased BP in up to 68% of patients (Yamasaki et al 2003).

The importance of hypertension as a cause of heart failure is further supported by the prevalence of hypertension as a comorbid condition in patients with heart failure in several settings. In primary care settings, approximately 48% of patients diagnosed with heart failure have been reported to have hypertension (Cleland et al 2002). Approximately 55% of patients in the Asian Sudden Cardiac Death in Heart Failure registry (Tromp et al 2018) and 66% of patients in the European Society of Cardiology Heart Failure Long-Term registry (Crespo-Leiro et al 2016) were diagnosed with hypertension and heart failure. Insurance claims data from the United States of America (USA) suggest that hypertension is the most commonly occurring comorbidity among Medicare beneficiaries with heart failure (Yancy et al 2013). Moreover, in clinical trials of heart failure, hypertension is one of the four most frequently cited comorbidities (Krum and Gilbert 2003).

In addition to evidence demonstrating the importance of hypertension as a cause of heart failure in longitudinal studies or in cross-sectional analyses of clinical trials of heart failure patients, in several national clinical audits or surveys, heart failure is frequently attributed to hypertension (rather than hypertension simply being identified as a comorbid condition). Indeed, in a national registry in the USA up to 30% of patients with heart failure had a hypertensive aetiology (Sweitzer et al 2008). Moreover, in European or USA studies or surveys of patients with acute heart failure, hypertension was the primary cause of heart failure in 11–23% of patients (Nieminen et al 2006, Gheorghiade et al 2006). Large registries in other countries have similarly reported a high prevalence of hypertensive heart failure with remarkably high prevalence rates noted in some countries. Indeed, in Korea, 37% of patients with heart failure had hypertension listed as the cause (Choi et al 2011).

The contribution of hypertension to heart failure is further supported by evidence of the impact on the development of heart failure when hypertension is prevented. In community-based studies, prevention of hypertension during middle age substantially prolonged heart failure-free survival (Lloyd-Jones et al 2002). Men and women without hypertension at 45 years of age live on average 35 years and 38 years respectively without incident heart failure. As compared to those with hypertension, those without hypertension at this age live on average an additional 3 to 15 years longer free of heart failure (Ahmad et al 2016). Thus, in the absence of hypertension by 45 and 55 years of age, there is an approximately 86% lower risk for incident heart failure in men and women respectively across the remaining life course (Ahmad et al 2016).

*1.1.1 Antihypertensive therapy and the prevention of heart failure*

The importance of BP in the development of heart failure is not only highlighted by epidemiological evidence, but also by a number of major clinical trials demonstrating the ability of antihypertensive therapy to prevent the development of heart failure (Dahlof et al 1991; Kostis et al 1997; MRC Working Party Medical Research Council 1992). This effect is consistent across all classes of antihypertensive agents. However, there is some evidence to suggest that for a given reduction in BP, some antihypertensives are more effective than others in preventing heart failure. In this regard, in the SHEP (Systolic Hypertension in the Elderly) clinical trial (SHEP Cooperative Research Group 1991) as well as in the HYVET (Hypertension in the Very Elderly Trial) clinical trial (Beckett et al 2008) there was a greater than 50% reduction in the risk of heart failure in hypertensives treated with thiazide-like diuretic therapy as compared to placebo. In this regard, the ability of thiazide-like diuretics as a group to prevent heart failure was noted in 10 randomized controlled trials to be clearly superior (20% better risk reduction) to that of all other antihypertensives (Thomopoulos et al 2016). With respect to differential effects of BP lowering agents on heart failure, there have also been suggestions that similar to their efficacy in the treatment of heart failure, β-adrenoreceptor blockers may also be more effective at preventing heart failure in hypertension. However, in a meta-analysis of 12 randomized controlled landmark clinical

trials involving over 100 000 patients with hypertension, β-adrenoreceptor blockers as compared to placebo resulted in a 23% reduction in heart failure risk (Bangalore et al 2008), an effect that was attributed entirely to BP lowering. Is there evidence that alternative classes of antihypertensive agents may have differential effects on the risk of heart failure for a similar degree of BP reduction? In this regard, in a Cochrane meta-analysis, calcium-channel blockers (CCBs) were noted to increase the risk of heart failure events by 37% as compared with diuretics (Chen et al 2010). However, a subsequent meta-analysis showed that BP lowering with CCBs is as efficacious as BP lowering by other antihypertensive drugs in preventing new onset heart failure (Thomopoulos et al 2016). In that study (Thomopoulos et al 2016) the authors reported that the inferiority of CCBs may depend to a large extent, on an unequal use of additional antihypertensive drugs. Nevertheless, further studies have similarly suggested that not all antihypertensives are as efficacious as others at preventing the onset of heart failure despite an ability to lower BP. In this regard, in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study, hypertensives treated with alpha-blocker (doxazosin), compared with the chlorthalidone (thiazide-like diuretic), had double the risk of heart failure (Coordinators for the ALLHAT Collaborative Research Group 2002). However, as with CCBs this finding may also depend on an unequal use of accompanying drugs. Indeed, in the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), doxazosin given as a third-line add-on drug did not increase the risk of heart failure (Chen et al 2010). Thus, overall, all major clinical trials in hypertension have demonstrated an ability of antihypertensive therapy to prevent heart failure. However, there appears to be a more beneficial role of thiazide-like diuretic therapy to prevent heart failure. As yet however, the mechanism of this effect has not been explained, with no evidence to support an ability of diuretic agents as a class to produce a sustained reduction in plasma volume in hypertension.

*1.1.2 Left ventricular dysfunction in the hypertensive heart*

Although hypertension may occur in approximately 40% of patients with heart failure with a reduced ejection fraction (HFrEF) (Davies et al 2001), a hypertensive aetiology is

more prevalent among patients with heart failure with a preserved ejection fraction (HFpEF) (Sweitzer et al 2008). Indeed, HFpEF is reported to be the dominant phenotype of heart failure in hypertensive heart disease (Tadic et al 2018). In comparison to HFrEF, the functional changes in the heart of patients with HFpEF are more complex. Although a wide variety of functional changes in both the myocardium and the coronary or peripheral vasculature are likely to contribute to HFpEF, including decreases in myocardial systolic function (Borlaug et al 2006, Brubaker et al 2006, Borlaug[a] et al 2010, Borlaug et al 2010), HFpEF is an abnormality of the diastolic period of the cardiac cycle. Indeed, the characteristic changes in the function of the left ventricle (LV) in HFpEF are those of LV diastolic dysfunction (LV DD) (Lee & Cooper 2009, Russo et al 2011, Burke et al 2014). In this regard, decreases in the active relaxation and an enhanced passive stiffness of the LV are fundamental features of LV DD (Zile et al 2004, Westermann et al 2008, Phan et al 2009, Westermann et al 2008, Selby et al 2011). The increases in ventricular stiffness (a left shift in the ventricular pressure-volume relationship at end diastole) and decreases in myocardial relaxation in HFpEF (Burke et al 2014, Mohammed et al 2012, Shah et al 2014, Westerman et al 2008, Zile et al 2004) enhance filling pressures in the LV for a given filling volume and the consequence is left and right sided heart failure. Important questions that arise are whether LV diastolic dysfunction is caused by the factors known to produce HFpEF and whether LV diastolic dysfunction heralds the onset of HFpEF?

Left ventricular DD or indices of an abnormal LV relaxation or increased filling pressures have been noted to either precede or predict the development of heart failure, particularly HFpEF (Bella et al 2002, Wan et al 2014, Wang et al 2003, Zile et al 2002, Westermann et al 2008, Aurigemma et al 2001, Kane et al 2011, Lam et al 2011, Redfield et al 2003, Schillaci et al 2002). Importantly, several large community-based studies have demonstrated a high prevalence of LV DD prior to the development of HFpEF and these functional changes in the LV are strongly related to several acknowledged risk factors for HFpEF, including hypertension (Redfield et al 2003, Zile et al 2004, Bursi et al 2006, Owan et al 2006, Russo et al 2011, Mohammed et al 2012, Burke et al 2014, Libhaber et al 2014).

Of significance, the most consistent associations between risk factors and LV DD are noted between age or hypertension and indices of LV diastolic function. What is the evidence to show BP effects on LVDD?

Many studies have shown associations between BP and measures of LV diastolic function. In this regard, either systolic (Masugata et al 2005, Abhayaratna et al 2008, Pavlopoulos et al 2008, Chung et al 2010, Hsu et al 2010) or diastolic (Tsioufis et al 2008, Al Jaroudi et al 2012, Hwang et al 2012, Libhaber et al 2014) BP are associated with early to-late (atrial) blood flow velocity across the mitral valve (E/A), a preload-dependent index of LV relaxation. Importantly, the BP that most strongly relates to E/A or LV DD in some large studies is diastolic rather than systolic BP (Tsioufis et al 2008, Libhaber et al 2009, Al Jaroudi et al 2012, Hwang et al 2012) Moreover, diastolic BP is associated with E/A independent of systolic BP whilst systolic BP is not related to E/A independent of diastolic BP (Libhaber et al 2014). However, E/A may initially decrease and then increase again as LV diastolic function progresses. This results in pseudo-normalisation of E/A. This may then progress to marked increases in E/A, indicative of a restrictive filling pattern and hence severe diastolic dysfunction. As E/A may decrease, normalise and then increase as LV diastolic function decreases, the focus on assessing LV diastolic function has more recently been on tissue Doppler indices of LV diastolic function.

In comparison to relationships between diastolic BP and E/A, E/e' (the ratio of trans-mitral blood flow velocity (E) to myocardial tissue lengthening (e') adjacent to the mitral valve in early diastole) (an index of LV filling pressures) or the preload-independent index of myocardial relaxation (e') are more frequently associated with systolic, but not diastolic BP (Mottram et al 2005, Pavlopoulos et al 2008, Russo et al 2010, Abhayaratna et al 2008, Chung et al 2010, Hsu et al 2010, Libhaber et al 2014). However, both systolic and diastolic BP may be associated with E/e' (Hwang et al 2012), but whether the relationship between diastolic BP and E/e' is independent of systolic BP, is uncertain. In major clinical studies including the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (Tapp et al 2010) antihypertensive therapy has been demonstrated to produce improvements in tissue Doppler

measures of DD (E/e' and e') and decreases in systolic BP best correlate with these changes (Almuntaser et al 2009). Importantly, in cross-sectional analysis of a community-based study with a high prevalence of obesity and type II diabetes mellitus, BP contributed substantially more to LV DD than did any other factor other than age (Millen et al 2014). Thus, LVDD is strongly dependent on BP and this effect is very likely to be age-dependent.

Despite the evidence in favour of BP being strongly associated with preclinical DD, the loading conditions responsible for the development of LV DD across the full adult age range have not been clearly described. In this regard, as will be discussed, several different factors contribute to LV loads at different ages across the full adult age range. Nevertheless, prior to work performed in the present thesis, the exact age at which these become important in contributing to LV DD was uncertain. Understanding the loading conditions (haemodynamic factors) responsible for LV DD across the full adult age range may allow for the identification of distinct targets for therapy at different ages to prevent or delay the development of HFpEF. What was the evidence available prior to the work performed in the present thesis on the age-dependent changes in haemodynamic factors responsible for LV loading and the effects of these loads on LV diastolic function?

## 1.2 The determinants of left ventricular load and their impact on LV diastolic function

It is well-accepted that load on the LV is determined by several factors which influence LV wall stress. In this regard, increases in vascular pressure generated in the proximal aorta and alterations in LV dimensions are the major determinants of LV wall stress. However, a number of studies have demonstrated associations between LV and vascular function beyond proximal aortic pressure. This is termed ventricular-vascular coupling and is generally determined by the relationship between LV and aortic end systolic elastance (slope of the end systolic volume-pressure relationship in the aorta and the LV). However, the calculation of aortic elastance is derived from end systolic pressure, which is determined by both pressure wave effects and aortic reservoir pressures (pressure determined by aortic elastance). Thus, the calculation of end systolic aortic elastance does not represent the true elastance of the aorta. Although reservoir pressures have more

recently been reported on, the calculation of reservoir pressures assumes that the diastolic period of the cardiac cycle is free of pressure waves, which is also an incorrect assumption (Westerhof et al. 2015). Thus, the concept of ventricular-vascular coupling beyond aortic pressure effects has never been proved. Consequently, in the present thesis I focussed my attention on the impact on LV function of aortic pressure effects.

Increases in systemic vascular resistance (SVR) is the dominant determinant of increases in LV wall stress during ejection (Chirinos et al 2012). Although it is possible that in some populations SVR increases across the adult lifespan, as discussed in aforementioned sections, diastolic BP which is strongly influenced by SVR, influences E/A and not tissue Doppler indexes of DD (myocardial e' or E/e') (Libhaber et al 2014). Moreover, more recent studies show that increases in systemic flow (stroke volume and hence cardiac output) rather than SVR account for increases in mean arterial pressure (MAP) and diastolic BP across the adult lifespan in Africa (Woodiwiss et al 2020). Thus, it is unlikely that age-related alterations in SVR account for decreases in LV diastolic function across much of the adult lifespan, particularly in communities of African ancestry. Indeed, in the Esklepios Study conducted in a middle-aged population sample in Europe, SVR played no role in mediating adverse effects on the LV (Chirinos et al 2013). Moreover, via an enhanced stroke volume, peak aortic flow rather than SVR determines increases in systolic BP in Africa (Woodiwiss et al 2020) and as indicated in aforementioned discussion, systolic BP is the primary determinant of decreases in myocardial e' and increases in E/e'. If SVR is not the primary factor that influences LV load and hence DD across the adult lifespan in Africa or in alternative populations, then what are the possible LV loading conditions that primarily determine age-related decreases in LV diastolic function?

From 50-60 years of age, the primary determinant of age-related increases in systolic BP is an increased pulse pressure (PP) caused by an enhanced incident or forward travelling pressure wave. This has been demonstrated in several large community-based studies including in the Framingham Heart Study (Mitchell et al 2010) and a community-based study in Africa (Booysen et al 2015, Hodson et al 2017). As indicated in previous

sections, as systolic BP (SBP) rather than diastolic BP (DBP) is the primary determinant of decreases in myocardial e' and increases in E/e', increases in early systolic pulsatile load, determined by forward travelling pressure waves is an important load that may explain age-related decreases in LV diastolic function. In this regard, increases in the forward travelling pressure wave may be generated by an enhanced stroke volume, which increases aortic flow during early systole, and this is particularly noticeable in populations in Africa (Woodiwiss et al 2020). Nevertheless, systemic flow in early systole interacts with the impedance to flow (resistance to flow in a pulsatile system) produced by the proximal aorta (characteristic impedance or Zc [resistance to flow in a pulsatile system in the absence of wave reflection]) and the product of Zc and peak aortic flow generate the forward travelling pressure wave (Nichols et al 2011, Phan et al 2016). What are the determinants of Zc?

Importantly, Zc is determined by two factors and these include increases in the stiffness and decreases in the diameter of the proximal aorta. In this regard, the aorta is normally an elastic organ which is able to absorb large amounts of energy produced by LV ejection. However, with aging and risk factors, the aorta stiffens and creates an impedance to flow. Although a lack of age-related increase in aortic diameter may play a role in producing increases in Zc (Mitchell et al 2003), age-related increases in aortic stiffness are thought to be the fundamental determinant of an increased Zc (Nichols et al 2011, Mitchell et al 2010). It is nonetheless argued that an increase in aortic diameter that normally occurs with aging may alter the impact of stiffness by increasing the degree of strain placed on collagen fibers in the aorta (Nichols et al 2011). The critical determinant of aortic stiffness is arteriosclerosis, which is determined by fragmentation of elastin fibers, an increase in collagen, an enhanced cross-linking of collagen and calcification of the aorta, all changes that are produced by uncontrolled conventional risk factors including hypertension (Lam et al 2010, Kovacic et al 2011, Wagenseil 2011, Mitchell, 2016). Although aortic stiffness is associated with LV DD or HFpEF (Hundley et al 2001, Kawaguchi et al 2003, Desai et al 2009, Mohammed et al 2012, Coutinho et al 2013, Kang et al 2010), forward wave pressures only begin to increase later in adult life (Mitchell et al 2010, Booysen et al 2015, Hodson et al

2017) and hence may not contribute to DD in early adult life. Moreover, increases in forward wave pressures and hence central arterial PP are closely paralleled by increases in brachial BP. Hence their adverse effects are likely to be readily detected and managed by measuring brachial BP and treating brachial BP to target. However, this may not be the case for alternative determinants of PP in central arteries. What are the alternative factors that could influence the load on the LV and which could play an important role in mediating LV DD? Moreover, are alterations in these factors readily detected at the brachial pulse?

Pulse pressure and hence systolic BP is generated not only by a forward travelling pressure wave, but by summation of forward waves with backward travelling pressure waves (Li et al 2017) (Figure 1.1). In this regard, the pressure wave produced by ventricular ejection is rapidly conducted in a forward direction down the arterial tree so that within a very short period (literally milliseconds), the pressure wave will have reached peripheral arteries. As with any conduit which transmits flow in a pulsatile manner, where tapering occurs (such as at points of bifurcation or narrowing of vessels in the arterial system), forward travelling pressure waves generated by intermittent flow in the conduit will reflect and generate multiple backward travelling pressure waves which return to the point of origin (O'Rourke and Yaginuma, 1984). As with the forward travelling pulsatile pressure waves, backward travelling pulsatile pressure waves travel at a very high speed in a normal aorta (around 3-6 m/sec). The high speed of wave travel of reflected (backward) waves will then result in the reflected waves returning to points in large arteries where the forward travelling pressure waves are at their antinodes and summation with the forward wave occur.

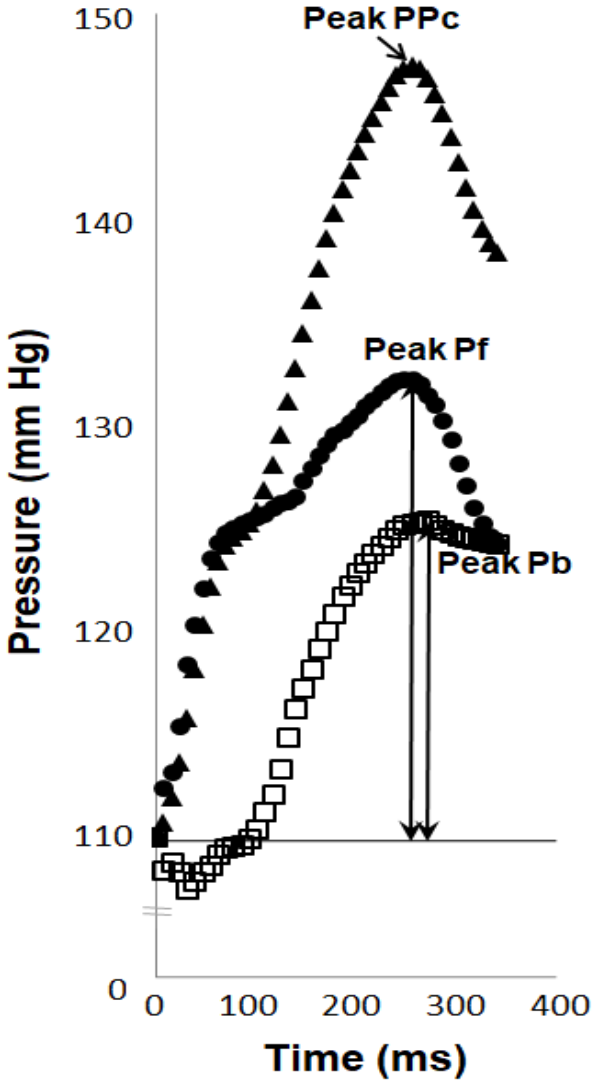


Figure 1.1 Aortic pressure wave and forward and backward travelling pressure waves showing (arrows) peak aortic pulse pressure (PPc), and the component pressure waves, peak forward (Pf) and peak backward (Pb) pressures. These are actual data obtained from central arterial pressure measurements and wave separation analysis performed from aortic pressure and flow assessments.

At points close to reflection sites summation of the backward travelling pressure wave with the forward wave is maximal (the two waves literally superimpose). However, the further from reflection sites (such as the point of origin of the forward travelling pressure wave in the proximal aorta), the more chance that the reflected wave will arrive at the forward wave's pressure node and hence summation of the two waves will be less than in the periphery. Where summation of forward and backward travelling waves occurs, the pulse will appear as a single pressure wave (Avolio *et al*., 2009; Phan *et al*., 2016). The further from the aorta (i.e. the closer to reflection sites) where maximal overlap between forward and backward travelling waves occurs, summation will generate what appears to be a single pulsatile wave. In contrast, the closer to the aorta (i.e. the further from reflection sites), where the least overlap between forward and backward waves occurs, the pulse will appear more as two discernible waves that have coincided with a first and second systolic shoulder (Figure 1.1). The consequence of these effects is that while backward travelling pressure waves in the periphery are determined by wave reflection in one peripheral bed only (e.g, wave reflection in forearm vessels will determine the brachial pulse), backward waves in central arteries are determined by the sum of numerous reflected waves returning from multiple vascular beds. Importantly, the backward wave in central arteries when transmitted outward to the brachial pulse, appears as a second systolic shoulder with a lower amplitude than the first systolic shoulder. Thus, alterations in backward wave pressures in central arteries are not detected at the brachial pulse. Hence, if backward wave pressures cause increases in LV afterload, these effects will not be indexed by brachial BP measurements.

If the speed of wave reflection is sufficiently slow then backward travelling pressure waves will arrive well after forward waves in the aorta and add to or augment diastolic more than systolic BP. This occurs in childhood when the aorta is very elastic and explains central arterial waveforms in some mammals with very elastic aorta or where a longer distance for wave travel exists (Nichols et al 2011). The advantage of this system is that it will promote coronary blood flow which largely occurs in the diastolic period of the cardiac cycle and which strongly depends on the pressure gradient across the coronary bed. However, in most

human adults from as early as 16 years of age the speed of wave travel is sufficiently fast that backward wave pressures will arrive in systole and thus summate with the forward travelling pressure wave. In this circumstance, backward waves thus augment aortic pulse pressure and are thus considered as essential determinants of peak aortic systolic BP (Agabiti-Rosei et al 2007, Avolio et al 2009). What are the determinants of backward wave pressures?

Through Newton's 1st (inertial forces) and 3rd (for every action there is an equal and opposite reaction) Laws of Motion the major determinant of maximal backward wave pressure (Pb in figure 1.1) is the peak pressure generated by the forward travelling pressure wave (Pf in figure 1.1). Thus, as Pf increases, so does Pb. This relationship has rendered the opinion that the primary target to reduce pulse pressure should always be Pf as reductions in Pb will automatically follow. However, there is now significant evidence that strong determinants of Pb are arteriolar tone and vascular tone in more proximal arteries (Cecelja et al 2009, Liao et al 2011). In this regard, to identify the role of vascular tone as a determinant of wave reflection obviously requires an approach that excludes the effects of aortic forward wave pressures on reflected wave pressures. To do this, reflection magnitude (RM) is calculated as the percentage Pb/Pf. Importantly, with aging RM increases from young adulthood to middle age and this change is independent of mean arterial pressure and hence generally considered to be independent of arteriolar tone (Hodson et al 2017). Are backward wave pressures associated with LV diastolic function?

Importantly, reflected or backward wave pressures are independently associated with LVDD and HFpEF (Weber et al 2006, Weber et al 2008, Ikonomidis et al 2008, Hashimoto et al 2006, Chirinos et al 2013, Peterson et al 2016). As reflected (backward) wave pressures and associated increases in late systolic load increase incrementally across the full adult lifespan (Namasivayam et al 2009, Hodson et al 2017), and are related to LV diastolic function (Weber et al 2006, Hashimoto et al 2006, Weber et al 2008, Ikonomidis et al 2008, Chirinos et al 2013, Peterson et al 2016), reflected wave pressures may play an important role in contributing to LVDD and hence the development of HFpEF across the adult lifespan

starting from a young adult age. This may be particularly important in groups of African ancestry where the adverse effects of backward (reflected) wave pressures on the LV may be more significant than forward wave pressures (Booysen et al 2015, Sibiya et al 2015). Moreover, reflection magnitude (Pb/Pf expressed as a proportion), which increases largely across the early adult lifespan and indexes reflected wave effects beyond forward wave effects (see aforementioned discussion), has been demonstrated to be an independent predictor of heart failure beyond several BP measurements in the Multiethnic Study on Atherosclerosis (Chirinos et al 2012). Nevertheless, brachial and central aortic pulse pressure largely increase later in adult life when the forward pressure wave begins to increase (Namasivayam et al 2009, Hodson et al 2017) and this effect is noted across ethnic groups (Hodson et al 2017). Hence, there is question as to the role of wave reflection as a cause of significant damage in early adult life. As age-related changes in different aspects of LV load begin at different ages, studying the impact on LV diastolic abnormalities across the full adult age range may provide insight into the age at which these effects are initiated and the extent to which they occur at different ages. In this regard, targeting relevant loading conditions at appropriate ages may better prevent the development of DD and consequently HFpEF.

In the present thesis, we hypothesized that because backward wave pressures consistently and linearly increase across the adult lifespan starting at a young adult age, that LV diastolic dysfunction, which shows similar linear changes across the full adult lifespan, would be strongly determined by backward wave pressures. If this is so, because increases in backward wave pressures are undetectable at the brachial pulse, this would suggest that intense brachial BP lowering would be required. Through the impact of forward on backward wave pressures (see aforementioned discussion), only intense brachial BP reduction would ensure that BP in central arteries remains within normal ranges. This would support more recent approaches to BP reduction (The Sprint Trial Group, 2021) which show improved outcomes, particularly for heart failure, in older hypertensives with intense brachial BP lowering. If backward wave pressures largely explain LV diastolic dysfunction and heart

failure, intense brachial BP reduction in the SPRINT study may have resulted in improved outcomes by achieving better control of central arterial BP. Nevertheless, at present it is uncertain whether backward wave pressures are indeed primarily responsible for LV DD. Hence, as part of the present thesis we assessed the impact of various determinants of afterload on LV diastolic function across the full adult age range in a community of African descent. These data are described in chapter 2 of the present thesis and have been published in the journal *Hypertension* (Bello et al, 2020).

**1.3 Left ventricular structural remodeling in hypertension**

If, as indicated in the aforementioned section, backward wave pressures are the primary cause of increases in LV afterload and LV diastolic dysfunction in hypertension, then as argued in the previous section, these effects will not be detected at the brachial pulse. Hence, it is important to have alternative measures that may index the impact of an uncontrolled central arterial BP on the LV. One such approach is to assess the degree of LV hypertrophy (LVH) either using electrocardiography such as may occur in resource-limited or primary care settings, or to employ echocardiography. In this regard, LVH and structural remodelling in the LV is a well-recognised consequence of uncontrolled LV afterload. Indeed, structural remodelling of the LV (hypertrophy and geometric changes) can be detected using a variety of clinical approaches recommended by guidelines to enhance risk prediction. However, more recent evidence from members of our research unit has questioned the role of these approaches to predict the development of LVDD and hence HFpEF in African populations, and indeed raises the question of the importance of structural remodelling as a necessary prelude to HFpEF in general. In the present section I will therefore review the general evidence to support a role for structural remodelling of the LV in the generation of LVDD and HFpEF and hence the use of these measures, and highlight the evidence to suggest that because structural LV remodelling may not be a necessary prelude to LVDD and HFpEF, that these measures may have a limited value in certain circumstances. I will then describe the hypothesis generated to explain why these measures may be limited to identify LV DD and hence predict the development of HFpEF.

Structural remodelling of the LV in hypertension is traditionally considered to be a compensatory response of the LV to chronic pressure overload. This is in accordance with the law of La Place where in a sphere, wall tension (stress) is proportional to the product of pressure and internal radius and inversely proportional to wall thickness. Therefore, hypertrophy of the LV (LVH) which results in an increased wall thickness to radius ratio (concentric LVH), maintains a normal LV wall stress in the face of increments in pressure generated within the LV cavity (Grossman et al 1975). Although considered to be a change that reduces wall stress, LV structural remodelling in hypertension is a well-recognised predictor of events beyond BP. As such, either electrocardiographic or echocardiographic assessments of LV structure are included in many major guidelines for the diagnosis and management of hypertension as an end organ change that enhances risk prediction (Chobanian et al 2003, Whitworth 2003, Williams et al 2004, Mancia et al 2007). Briefly, what is the evidence to support a role for these measures in clinical practice?

Several large population and clinical studies have demonstrated that LVH predicts cardiovascular outcomes beyond BP (Casale et al 1986, Ghali et al 1998, Levy et al 1990, Levy et al 1994, Verdecchia et al 1996, Verdecchia et al 2001, Gardin et al 2001, Drazner et al 2004) and a reduction of LV mass during antihypertensive therapy similarly predicts improved cardiovascular outcomes beyond BP changes (Mathew et al 2001, Devereux et al 2004, Okin et al 2004). Importantly, in-keeping with the notion that the structural changes in the LV in-part mediate adverse effects on the heart, a number of clinical studies have demonstrated that LVH is an independent predictor of the development of heart failure (Casale et al 1986, Levy et al 1990, Levy et al 1996, Gottdiener et al 2000, Gardin et al 2001, Aurigemma 2001). Nevertheless, the relationships between LVH and heart failure (Casale et al 1986, Levy et al 1990, Levy et al 1996, Gottdiener et al 2000, Gardin et al 2001, Aurigemma 2001) are not necessarily cause-effect relationships as there are no studies that have specifically targeted LVH therapeutically and demonstrated an ability to prevent the development of either HFpEF or HFrEF. Therefore, the role of LVH as a cause of heart failure remains uncertain.

*1.3.1 Does LVH cause LV diastolic dysfunction and HFpEF?: Cellular changes in the left ventricle*

There are several reasons why hypertensive LVH may contribute to LV diastolic dysfunction and hence HFpEF. In this regard, LVH may be associated with an increased myocardial oxygen demand (Kannel et al 1970, Strauer 1979, Kass et al 2004), but an accompanying proportionate increase in coronary blood flow may not occur due to limitations of coronary flow reserve (Marcus et al 1979, Cimini et al 1989, Lorell et al 1987, Gosse and Clementry 1995). Indeed, there is significant evidence to show that microvascular changes in the hypertensive LV may contribute toward HFpEF and LV diastolic dysfunction (González et al 2018, Camici et al 2020). As a consequence of alterations in myocardial oxygen supply-to-demand ratios and thus a reduced capacity of the sarcoplasmic reticulum to sequester calcium (an energy requiring process), hypertensive LVH may lead to impaired filling of the LV due to a decreased early-diastolic relaxation (Gibson et al 1980, Shapiro and McKenna 1984, Calderone et al 1995, Kass et at 2004). Furthermore, subsequent to reparative myocardial fibrosis, induced by tissue necrosis possibly in-part as a consequence of alterations in myocardial oxygen supply-to-demand ratios (Tsotetsi et al 2001), hypertensive LVH may be associated with an increased myocardial diastolic stiffness (Conrad et al 1995) and a diminished late-diastolic compliance, changes which could contribute towards LV diastolic chamber dysfunction in hypertensive LVH. In addition, in LVH the hypertrophic process results in re-expression of the cardiomyocyte fetal gene programme which includes repression of genes important for myocardial relaxation (e.g SERCA2) (Frohlich et al 2010). Moreover, metabolic alterations may occur in LVH which ultimately, in conjunction with an increased demand for energy, also reduce the ability of cardiomyocytes to relax (González et al 2018). Although many of these cellular changes that could contribute to relaxation abnormalities or increases in passive stiffness may in-part occur as a consequence of processes that accompany LVH, the bulk of more contemporary evidence suggests that changes in the myocardium may account for LV diastolic dysfunction independent of LVH. What are these changes?

A host of more recent data (reviewed by González et al 2018) show that inflammatory changes causing oxidative stress-induced endothelial dysfunction, contribute to the production of fibrosis and overexpression or alterations in titin isoforms, both changes which will increase passive stiffness of the LV (González et al 2018). While many of the aforementioned changes (previous paragraph) may impair relaxation processes in-part through the increased energy requirements of a hypertrophied LV, alterations in diastolic properties on the LV produced at an endothelial level with consequent increases in fibrosis or alterations the characteristics of titin, are to the best of my knowledge not dependent on LVH. These findings are indeed in-keeping with the original descriptions many years ago of therapeutic benefits of antihypertensives on LV diastolic function (end diastolic compliance) without alterations in LV weight (Norton et al 1997). What is the clinical evidence therefore to support or refute a causal role of LVH in the pathophysiology of LV diastolic dysfunction?

*1.3.2 Does LVH cause LV dysfunction and HFpEF?: Clinical evidence*

There is no question that LVH and concentric LV remodelling in LVH are independently associated with LV DD. Indeed, LV DD may be seen in up to 84% of hypertensive individuals with LVH (Wachtell et al 2000). In contrast, only 11% to 20% of hypertensive patients have been reported to have LV DD in the absence of LVH (Phillips et al 1989, Dini et al 2013). However, the aforementioned estimates of the occurrence of LV DD in the presence of LVH were obtained at a time when more contemporary approaches (tissue Doppler imaging) to determining LV diastolic function were unavailable. In this regard, using contemporary assessments of diastolic LV function, DD has nevertheless been noted to be worse in patients with LVH as compared to those without LVH (Kattel et al 2016). These findings are therefore consistent with the notion that LVH naturally progresses to both DD and heart failure and more specifically, that concentric LVH progresses to HFpEF (Drazner 2011). These concepts have nonetheless been translated to indicate that the presence of LVH is essential for the development of LV DD and HFpEF. Although there is indeed substantial evidence to support the fact that LVH and concentric LV remodelling in-

part mediate LV DD, there is also considerable evidence to support a view that LV DD occurs separate from the hypertrophic process. What is this evidence?

Many patients with HFpEF do not have LVH (Lam et al 2007) despite the fact that hypertension is the dominant risk factor for this form of heart failure. Moreover, LV DD without LVH is an early manifestation of hypertensive heart disease (Messerli et al 2017). Furthermore, a marked dissociation has been noted between ethnicity and LV mass versus DD (Shantsila et al 2018), and a limited contribution of concentric LVH to DD in hypertensives more recently described (Nazário Leão et al 2018). In addition, it is mainly those with LVH who, in addition to a structural change in the LV, have biomarker evidence of increased loading conditions or myocardial damage produced presumably by increased loads, that progress to heart failure (Seliger et al 2015). Further, assigning those with LVH to concentric versus eccentric subtypes only moderately differentiates participants at increased risk of heart failure with a preserved versus reduced ejection fraction (Ho et al 2013). Also, in the ASCOT trial, the marked differences in treatment groups in improvements in LV diastolic function with antihypertensive therapy were unaffected by adjustments for LV mass index (Tapp et al 2010). In addition, in the LIFE study, a greater regression of LV mass noted in patients receiving the angiotensin II receptor blocker versus β-adrenoreceptor blocker-based therapy (Okin et al 2003) failed to translate into reduced heart failure in the angiotensin II receptor blocker treated group (Dahlof et al 2002). Nevertheless, in a pre-specified subgroup of 1195 patients with diabetes mellitus, there was a reduction in heart failure in the angiotensin II receptor blocker-treated arm of approximately 40%, as compared to the β-adrenoreceptor blocker group (Lindholm et al 2002). The inconsistencies in relationships noted between LVH and the regression thereof and LV DD nevertheless challenge the notion that LVH or associated structural remodelling processes are necessary changes in the generation of LV DD and the transition to HFpEF in hypertension. More recent findings in groups of African ancestry may caste some light on this question. What is this evidence and how may these data assist with our understanding of the role of hypertensive LVH and

concentric LV remodelling as an essential change responsible for LV DD and the transition to HFpEF?

*1.3.3 Does LVH cause LV dysfunction?: Insights from Africa*

Recent data from members of our research group suggest that although LVH and concentric LV remodelling do indeed play a role in LV DD (Peterson et l 2016, Bamaiyi et al 2019), that the structural changes in the LV fail to account for much of the adverse effect of BP on LV diastolic function (Bamaiyi et al 2019). In that study (Bamaiyi et al 2019) members of our research group demonstrated in a large community-based sample living in SOWEO South Africa, that in product of coefficient mediation analysis that most of the effects of conventional BP measured at the brachial artery on LV diastolic function are not explained by either LVH or concentric geometric LV remodelling. Our research group proposed in that study (Bamaiyi et al 2019) that this finding may be explained by the fact that LV diastolic dysfunction in hypertension occurs through an impact of BP effects that do not require either hypertrophy of cardiomyocytes or concentric remodelling to produce these effects These data are entirely consistent with many of the findings outlined in the previous section which segregate the impact of hypertension on diastolic dysfunction and LVH or geometric LV remodelling. However, it is difficult to understand why this segregation should occur as even if LV dysfunction does not require LVH or concentric LV remodelling, BP in hypertension is thought to mediate both effects. Thus, these changes should theoretically occur in parallel. However, additionally at around the same time, members of our research group also demonstrated that concentric geometric LV remodelling could not be explained, by BP effects, but rather were strongly associated with inflammatory changes (Norton et al 2019). These data therefore provided a clue as to why LVH may not predict LV dysfunction and that is, that LVH and concentric LV remodelling are strongly driven by factors other than BP. One potential explanation for these findings (Bamaiyi et al 2019) is that LVH is not only determined by BP, but by the work performed by the heart. What are the factors that determine workload and what is the evidence to support a role for workload as opposed to

afterload as a significant cause of LVH? In this regard, a number of studies support an important role for workload as opposed to simply afterload as a cause of LVH.

*1.3.4 Workload rather than afterload also determines LVH*

In keeping with conventional physical laws, the work performed by the heart is the product of force and distance. In this regard, the major factor that determines the force is systolic BP and the distance is that determined by the volume of blood ejected from the heart (stroke volume). The workload on the LV can therefore be estimated from stroke work, which is the product of systolic BP and stroke volume. That the workload on the LV is a critical factor that determines LVH has long been recognised and explains the marked physiological LVH that may occur in athletes or many volume-overload states where LV dysfunction does not occur and may even be improved. While pressure overload effects (afterload) are thought to mediate concentric LVH, volume overload states which cause an increased stroke volume and through an enhanced aortic flow, an increased SBP, are thought to be largely responsible for eccentric LVH. What is the impact of workload as opposed to pressure load in hypertension on cardiac function?

A well-recognised hypothesis proposed some years ago is that the transition to heart failure in hypertension is from a compensated state of hypertrophy, where LVH is in-keeping with increases in work load produced by an increased SBP, to a state of decompensation where LVH exceeds the workload (de Simone et al 1998). The degree of LVH that exceeds the workload is called “inappropriate” LVM [$LVM_{inappr}$]) (de Simone et al 1998). Indeed, despite the limited data to show relationships between LVH and LV systolic chamber dysfunction, a number of studies have demonstrated an inverse relationship between $LVM_{inappr}$ and LV systolic function (Palmieri et al 1999, Palmieri et al 2001, Celentano et al 2001, de Simone et al 2004, Chinali et al 2006, Chinali et al 2007, Cioffi et al 2011; Libhaber et al 2013). Moreover, a strong relationship has been noted between antihypertensive treatment-induced decreases in $LVM_{inappr}$ and increases in EF independent of LVM or LVM index (Woodiwiss et al 212). These data provide support for the notion that LVH is indeed a cause of LV systolic chamber decompensation, but that this relationship only occurs when

LVH exceeds that predicted from work-load. However, although several studies have demonstrated relationships between LV mass and LV diastolic function (see aforementioned discussion), there is limited data to show relationships between only that component of LVH that exceeds workload and LV diastolic function. This is indeed in-keeping with several types of volume overload states, including in physiological LVH (the athletic heart), where LV diastolic function is not a feature of these forms of hypertrophy. This, of course raises the question of the implications of LVH for LV diastolic function when hypertension is strongly driven by a volume-dependent state?

As indicated in aforementioned sections, recent data produced by our group demonstrates unequivocal and striking age-related increases in stroke volume, cardiac output and peak aortic flow as a cause of hypertension in groups of African ancestry living in Africa (Woodiwiss et al, 2020, Mmopi et al 2020). Although the effects of increases in systemic flow on BP do not occur in isolation and increases in BP are also accounted for by age-related increases in proximal aortic characteristic impedance (Zc), and decreases in total arterial compliance (TAC), the contribution of increases in systemic flow to hypertension across the adult lifespan is at least as great as Zc and TAC (Woodiwiss et al, 2020, Mmopi et al 2020). In these studies, the increases in systemic flow accounted for age-related decreases in plasma renin concentrations and hence for low renin hypertension (Woodiwiss et al 2020), a prevalent form of hypertension in Africa. This raises the question as to how much of LVH in hypertension in Africa is driven by volume-dependent effects on workload. If so, this also raises the question of whether LV mass is unable to account for much of the impact of BP on LV diastolic function in Africa (Bamaiyi et al 2019) because LVH is largely determined by stroke work, rather than afterload effects on the LV in Africa. If so, the inability of LV mass to account for much of the effect of BP on LV diastolic dysfunction may be specific to some forms of hypertension (volume-dependent forms of hypertension where increases in systemic flow drive the hypertension). This may nevertheless be only in those with eccentric LVH, as eccentric LVH is thought to be a consequence of a volume-dependent form of hypertension. Does an eccentric versus a concentric geometry distinguish

whether LVH accounts for LV diastolic dysfunction in volume-dependent hypertension in Africa? In the study where members of our group demonstrated only a modest contribution of LV mass to the adverse effects of BP on LV diastolic function, concentric LV remodelling also failed to account for much of the effect of BP on LV diastolic function (Bamaiyi et al 2019).

As electrocardiographic or echocardiographic measures of LVH are employed to enhance risk prediction, a better understanding of the role of LVH as a mediator of LV diastolic function and hence the progression to HFpEF in volume-dependent populations is required. This is particularly important if the haemodynamic load (such as backward wave pressures) that account for decreases in LV diastolic function, cannot be adequately detected at the brachial pulse. Indeed, as indicated in previous discussion, this is a central hypothesis of the present thesis. Hence, as part of the present thesis we therefore aimed to determine the extent to which the impact of stroke work (SW) on LV mass limits the ability of LV mass to detect BP related decreases in tissue Doppler measures of systolic and diastolic LV function in a community of African ancestry. We hypothesized that the inability of LVH to account for the adverse impact of BP on LV diastolic function in groups of African ancestry could be explained by a dominant role of volume-induced increases in stroke volume and hence stroke work on LVH. These data are described in chapter 3 of the present thesis and have been accepted for publication in the *Journal of Hypertension* (Bello et al, 2021).

### *1.3.5 Concentric versus eccentric left ventricular hypertrophy*

As alluded to in aforementioned sections, structural remodelling of the LV in hypertension includes not only hypertrophy of the heart, but also geometric changes defined by disproportionate alterations in mass or wall thickness relative to internal volumes or diameters. If LVH *per se* is an unreliable index of the extent of LV dysfunction caused by increases in central arterial changes that cannot be detected at the brachial pulse, then perhaps the geometric LV remodeling process may better index these LV functional changes? In this regard, several studies have demonstrated that as compared to a normal LV geometry, concentric LV remodelling, as indexed by either an increased wall thickness-

to-internal radius in the LV short axis (relative wall thickness-RWT) or an increased LV mass (LVM)-to-volume ratio, predicts cardiovascular risk beyond that noted in those with a more eccentric LV geometry (Koren et al 1991, Koren et al 1991, Verdecchia et al 1995, Krumholz et al 1995, Pierdomenico et al 2004, Muiesan et al 2004, Milani et al 2006, Bluemke et al 2008, Bang et al 2014, Tsao et al 2015, Cuspidia et al 2015). Conventional thought is that a more concentric LV (remodelling or hypertrophy) indexes a worse pressure load on the heart, while a more eccentric LV more of a volume load. However, the implications of a concentric LV beyond LVH in populations generally considered to have prevalent volume-dependent hypertension, are uncertain.

In volume-dependent hypertension, the volume overload produces an increased stroke volume and current thinking is that as long as the increased stroke volume has not translated into a poor BP control, eccentric LVH is likely and this form of hypertrophy may not always predict a worse outcome than those without LVH (Bang et al 2014, Cuspidia et al 2015). The remodelling process is therefore thought to provide information as to the pathophysiological mechanism that requires targeting with the presence of concentric LVH suggesting a worse BP control. Nevertheless, a high prevalence of concentric LVH as identified from RWT assessments in the short axis of the LV (Bamaiyi et al 2019, Norton et al 2019) has been reported in a community recently demonstrated to show prevalent volume-dependent, low renin hypertension strongly associated with an age-related increase in LV filling volumes and hence SV (Woodiwiss et al 2020, Mmopi et al 2020). Importantly, a strong age-related increase in LV mass index, a change well recognised as contributing to concentric remodelling, has also been noted (Bello et al 2020). These data therefore raise the question as to whether a more concentric LV, as identified from short axis dimensions, indeed reflects less of a volume and more of a pressure overload state in those with volume-dependent forms of hypertension?

In order to preserve systolic chamber function concentric LVH may occur as a response to decreases in intrinsic myocardial systolic function, a change frequently noted in populations with prevalent volume-dependent hypertension (Libhaber et al 2013, Woodiwiss

et al 2012). Moreover, concentric LV remodelling may accompany LV diastolic dysfunction, changes also frequently noted in populations with prevalent volume-dependent hypertension (Bamaiyi et al 2019, Bello et al 2020). In this regard, the cellular mechanisms responsible for diastolic dysfunction in hypertension may cause a concentric LV (Badenhorst et al 2003). Hence, concentric LVH may be the consequence of functional abnormalities in the LV (either systolic or diastolic dysfunction) rather than a consequence of more of a pressure rather than volume overload.

To address these issues, in the present thesis we therefore also aimed to identify the haemodynamic and LV functional correlates of concentric LV remodeling beyond hypertrophy in the aforementioned community of African ancestry living in South Africa with a high prevalence of volume-dependent, low renin hypertension (Woodiwiss et al 2020, Mmopi et al 2020). If concentric LV remodeling is explained by the impact of a pressure overload produced by increases in backward wave pressures undetectable at the brachial pulse, then the LV remodeling process may provide information that enhances the detection of those at risk for LV diastolic dysfunction. However, if concentric LV remodeling is determined as much by a volume as a pressure overload, then the LV geometry will not enhance the ability to detect LV diastolic dysfunction. In the present thesis I therefore evaluated whether because of the dominant role of volume-dependent mechanisms explaining hypertension in Africa, that both concentric and eccentric LVH are determined by increases in stroke volume and that concentric LV remodeling is more a compensatory structural change that occurs in response to LV dysfunction. These data are described in chapter 4 of the present thesis and have been accepted for publication in the *American Journal of Hypertension* (Bello et al, 2021).

## 1.4 Problem statement

Hypertension in an aging population is the dominant cause of a reduced LV diastolic function and hence the progression to HFpEF. Presently it is assumed that the haemodynamic factors associated with hypertension that account for HFpEF are those changes that occur in the elderly or very elderly and that the haemodynamic factors causing

progressive changes in the LV responsible for HFpEF only begin at an older age. However, several haemodynamic changes are now recognized as contributing to age-related increases in BP starting at a young adult age and these changes are particularly striking in groups of African descent. In this regard, age-related increases in wave reflection start at an early adult age and are not detected in the pulse at the brachial artery. Thus, if reflected wave pressures are the primary determinants of LV diastolic dysfunction, then alternative indices of the adverse effects of afterload, other than brachial BP, are required to detect these effects. Furthermore, to control increases in central arterial pressures caused by an enhanced wave reflection, intense brachial BP reduction would be required. Thus, identifying the haemodynamic factors responsible for progressive age-related diastolic functional changes in the LV may provide better insights into approaches that prevent HFpEF.

Conventional thought is that to identify those hypertensives at risk for heart failure at any age, risk assessment can be enhanced by detecting LVH or concentric remodelling using electrocardiographic or echocardiographic approaches. These measures are thought to provide early signals that identify a need for more careful BP control and hence prevent the progression to heart failure. If reflected wave pressures are the primary cause of LV diastolic dysfunction, then the impact of afterload on LV function will not be adequately identified from BP measured at the brachial pulse. In this circumstance the use of measures of LVH or geometric LV remodelling may be critical to identify those with uncontrolled central arterial pressures who require intense brachial BP reduction. However, in groups of African ancestry there is now evidence to show that neither LVH nor concentric LV remodelling can adequately account for the adverse effects of BP on LV diastolic function. Whether this may be explained by the recent finding that in this ethnic group hypertension is strongly driven by a volume overload state and hence that LVH is determined more by workload than afterload, is unknown. If this is indeed the case, then LVH (concentric or eccentric), would not serve as an adequate early signal for predicting the risk for LV DD and the progression to HFpEF.

## 1.5 Hypotheses

In the present thesis we therefore hypothesized the following:

1. Those abnormalities of LV diastolic function that ultimately translate into HFpEF, begin at an early adult age in groups of African descent and continue across the adult lifespan and that wave reflection, which is not detected at the brachial pulse, explains most of these effects.

2. That in groups of African descent where hypertension is strongly volume and systemic flow-dependent, that while LV diastolic functional changes are accounted largely by the adverse effects of BP, LVH is accounted for largely by the impact of increases in workload. As a consequence, LVH is unable to explain much of the effects of BP on LV diastolic function.

3. That in groups of African descent where hypertension is strongly volume and systemic flow-dependent, that concentric LVH is determined as much by volume-dependent haemodynamic changes as eccentric LVH, and that concentric as opposed to eccentric LVH is more of a response to functional changes in the myocardium than on differences in haemodynamic loads.

## 1.6 Aims

The aims of the present thesis are therefore as follows:

1. To identify the dominant age-related haemodynamic factors responsible age-related decreases in LV diastolic function across the adult lifespan in a community of African ancestry. These data are described in chapter 2 of the present thesis and have been published in *Hypertension* (Bello et al 2020).

2. To determine whether the impact of stroke work on LV mass modifies the ability of LV mass to account for BP effects on LV diastolic function in a community of African ancestry where hypertension is strongly driven by increases in stroke volume. These data are described in chapter 3 of the present thesis and have been accepted for publication in the *Journal of Hypertension* (Bello et al, in-press).

2. To determine whether in a community of African ancestry where hypertension is strongly driven by increases in stroke volume, whether LV geometry (concentric versus eccentric LVH) is determined by variations in loading conditions or is a compensatory response to decreases in LV function. These data are described in chapter 4 of the present thesis and have been accepted for publication in the *American Journal of Hypertension* (Bello et al, in-press).

# Chapter 2

## Hemodynamic Determinants of Age versus Left Ventricular Diastolic Function Relations Across the Full Adult Age Range.

This chapter has been published in the journal *Hypertension*

Bello H, Norton GR, Peterson VR, Mmopi KN, Mthembu N, Libhaber CD, Masiu M, Da Silva Fernandes D, Bamaiyi AJ, Peters F, Sareli P, Woodiwiss AJ. (2020). Hemodynamic Determinants of Age Versus Left Ventricular Diastolic Function Relations Across the Full Adult Age Range. *Hypertension,* 75**,** 1574-1583.

## 2.1 Abstract

The relative contribution of loading conditions at different ages across the full adult lifespan to decreases in left ventricular (LV) diastolic function is unclear. Using central arterial pressure, and aortic velocity and diameter measurements in the outflow tract, we determined the contribution of systemic vascular resistance (SVR), pressures generated by the product of characteristic impedance (Zc) x aortic flow (Q), ($P_{QxZc}$) and backward wave pressures (Pb) to LV diastolic function (echocardiography) in a community sample across the full adult lifespan (n=605). Starting from early adulthood, stepwise age-related increases in LV filling pressures (E/e') and decreases in myocardial relaxation (e') were noted ($p<0.0001$). Before 50 years of age, prior to when $P_{QxZc}$ positively correlates with age, Pb, but not SVR was independently associated with LV mass index (LVMI) ($p<0.002$), E/e' ($p<0.002$) and e' ($p<0.05$). Moreover, in those over 50 years of age, when $P_{QxZc}$ positively correlates with age, again Pb, but neither $P_{QxZc}$ nor SVR was independently associated with LVMI ($p<0.01$), E/e' ($p<0.001$) and e' ($p<0.001$). The contribution of Pb to age-related decreases in LV diastolic function was as strong in those younger as compared to older than 50 years of age and poorly indexed by brachial BP. In conclusion, a striking age-related deterioration in LV diastolic function begins at an early adult age and Pb is the dominant hemodynamic factor that accounts for this relationship. Age-related increases in Pb in young adults contribute as much to functional abnormalities ultimately responsible for LV diastolic dysfunction in hypertension as at an older age, effects poorly indexed by brachial BP.

## 2.2 Introduction

Heart failure with a preserved (normal) ejection fraction (HFpEF) presently has no treatment with established benefits (Owan et al 2006, Bhatia et al 2006, Lee et al 2009, Borlaug and, Borlaug and Redfield 2011, Pitt et al 2014). Identifying targets to prevent the transition to this form of heart failure is therefore a priority. Hypertension is well recognized as a major cause of HFpEF. Indeed, an increase in blood pressure (BP) is the dominant risk factor for reductions in left ventricular (LV) diastolic function (Millen et al 2014, Bamaiyi et al 2019) the functional cardiac change mainly responsible for HFpEF (Zile et al 2004, Westermann et al 2008, Mohammed et al 2012, Burke et al 2014, Shah et al 2014, Wan et al 2014). In this regard, LV diastolic dysfunction (DD) is determined by a combination of increases in LV stiffness and relaxation abnormalities (Zile et al 2004, Westermann et al 2008, Mohammed et al 2012, Burke et al 2014, Shah et al 2014, Wan et al 2014). Importantly, the impact of hypertension on the development of HFpEF is strongly age-dependent. However, the exact loading conditions at different ages that ultimately contribute to the development of DD and the extent of these effects at different ages is poorly understood.

Several factors load the LV including increases in systemic vascular resistance (SVR) which is the dominant determinant of increases in LV wall stress during ejection (Chirinos et al 2012). Although SVR increases across the adult lifespan, diastolic BP which is strongly influenced by SVR, influences E/A and not tissue Doppler indexes of DD (Libhaber et al 2014). Alternatively, increases in early systolic pulsatile load, determined by forward travelling pressure waves (generated by the product of aortic stiffness-associated increments in characteristic impedance [Zc] and peak aortic flow) may also enhance LV load (Nichols et al 2011, Phan et al 2016). Although aortic stiffness is associated with DD or HFpEF (Hundley et al 2001, Kawaguchi et al 2003, Desai et al 2009, Kang et al 2010, Mohammed et al 2012, Coutinho et al 2013), forward travelling pressure waves only begin to increase later in adult life (Namasivayam et al 2009, Hodson et al 2017) and hence may not contribute to DD in early adult life. However, reflected (backward) wave pressures and

associated increases in late systolic load, which increase incrementally across the full adult lifespan (Namasivayam et al 2009, Hodson et al 2017), are also related to LV diastolic function (Weber et al 2006, Hashimoto et al 2006, Weber et al 2008, Ikonomidis et al 2008, Chirinos et al 2013, Peterson et al 2016), and may play an important role across the adult lifespan starting from a young adult age. Nevertheless, brachial and central aortic pulse pressure (PP) largely increase later in adult life when the forward travelling pressure wave begins to increase (Namasivayam et al 2009, Hodson et al 2017) and hence there is question as to the role of wave reflection as a cause of significant damage in early adult life. As age-related changes in different aspects of LV load begin at different ages, studying the impact on LV diastolic abnormalities across the full adult age range may provide insight into the age at which these effects are initiated and the extent to which they occur at different ages. In this regard, targeting relevant loading conditions at appropriate ages may better prevent the development of DD and consequently HFpEF. Hence, in the present study we assessed the impact of various determinants of afterload on LV diastolic function across the full adult age range in a community of African descent with a high prevalence of LV hypertrophy (LVH) and DD (Bamaiyi et al 2019).

## 2.3 Methods

### *2.3.1 Study group*

The present study was conducted according to the principles outlined in the Helsinki declaration. The Human Research Ethics Committee (Medical) of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69, M12-04-108 and M17-04-01). Participants gave informed, written consent. The data are available from the corresponding authors upon reasonable request. The present study design has previously been described (Woodiwiss et al 2009, Norton et al 2012, Millen et al 2014, Libhaber et al 2014, Booysen et al 2015, Peterson et al 2016; Hodson et al 2017, Bamaiyi et al 2019). In the present sub-study 605 participants from randomly recruited (from the population census figures of 2001) families of black African descent (Nguni and Sotho chiefdoms) from the South West Township (SOWETO) of Johannesburg, South Africa, with

siblings older than 16 years of age with high-quality velocity assessments in the outflow tract were evaluated.

*2.3.2 Clinical and demographic information*

A questionnaire was administered to obtain demographic and clinical data (Woodiwiss et al 2009). Height and weight were measured using standard approaches and participants were considered to be overweight if their body mass index (BMI) was ≥25 kg/m$^2$ and obese if their BMI was ≥30 kg/m$^2$. Laboratory blood tests of renal function, liver function, blood glucose, hematological parameters, and percentage glycated hemoglobin (HbA1c) were performed. Diabetes mellitus (DM) was defined as the use of insulin or oral glucose lowering agents or an HbA1c value greater than 6.5%. High quality office brachial blood pressure (BP) measurements were obtained in the seated position and after 5 minutes of rest, by a trained nurse-technician using a standard mercury sphygmomanometer as previously described (Woodiwiss et al 2009) and according to guidelines. The mean of 5 measurements obtained at least 30 seconds apart was taken as office BP. Hypertension was defined primarily as a mean office BP≥140 mm Hg systolic or ≥90 mm Hg diastolic BP or the use of antihypertensive medication. In addition, however, in those participants not on therapy, 24-hour ambulatory BP monitoring (SpaceLabs model 90207) was performed as previously described (Woodiwiss et al 2009) also to diagnose hypertension (≥130/85 mm Hg for the 24-hour period).

*2.3.3 Arterial hemodynamic assessments*

Arterial function was determined from central arterial pressure recordings obtained from pulse wave analysis (Norton et al 2012, Booysen et al 2015, Peterson et al 2016, Hodson et al 2017) and aortic velocity and diameter assessments obtained in the outflow tract (Mitchell et al 2010). After participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry 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). The

pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. The peripheral pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphygmoCor software. Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. Whilst central arterial pressure waveforms were obtained aortic velocity and diameter measurements were obtained by an experienced observer (AJW) in the left lateral decubitus position using an Acuson SC2000 Diagnostic ultrasound system (Siemens Medical Solutions, USA, Inc.). Velocity waveforms were obtained in the 5-chamber view. Aortic diameter measurements were obtained just proximal to the aortic leaflets in the long axis parasternal view. The largest diameter recorded in early systole was employed to construct the flow waveform (Mitchell et al 2010).

*2.3.4 Aortic pressure wave components*

Aortic flow (Q) waveforms were generated from aortic velocity and diameter measurements. Taking care to avoid any overshoot of the image, the leading (outer) edge or the most dense, or brightest, portion of the spectral image of the velocity waveform was outlined using graphics software and using aortic diameter measurements from which cross-sectional area was determined, employed to construct a flow waveform. Characteristic impedance (Zc) was calculated in the time domain as change in pressure/change in flow from the foot of the pulse wave up until 95% of peak flow (Mitchell et al 2010, Segers et al 2017). Using Zc values and the flow and pressure waveforms, wave separation analysis was performed based on the following formulae: Forward wave pressure=(aortic PP + QxZc)/2 and Backward wave pressure=(aortic PP – QxZc)/2 (Westerhof et al 1972, Murgo et al 1981). Wave separation analysis was performed in the time domain based upon the consensus that this analysis can be conducted in either the time or the frequency domain (Segers et al 2017). We determined the peak pressures generated from the product of peak Q and Zc (Peak $P_{QxZc}$) (Phan et al 2016). Peak $P_{QxZc}$ rather than forward wave pressures were employed as $P_{QxZc}$ is that component of forward wave pressures driven by increases in

aortic stiffness and hence Zc rather than wave re-reflection (Phan et al 2016). Stroke volume was determined from the velocity-time integral of the aortic velocity wave and aortic root diameter using standard approaches. Systemic vascular resistance (SVR) was calculated from mean arterial pressure (MAP) and cardiac output (MAP=SVR x CO), assuming right atrial pressure = 0 mm Hg. Cardiac output was determined from SV x heart rate.

*2.3.5 Echocardiography*

Echocardiographic measurements were performed as previously described (Woodiwiss et al 2009, Norton et al 2012, Millen et al 2014, Libhaber et al 2014, Booysen et al 2015, Bamaiyi et al 2019, Peterson et al 2016) by two experienced observers (AJW and CDL) with a low degree of intra- and inter-observer variability, with the participants in the partial left decubitus position. Details of the measurements have previously been described (Woodiwiss et al 2009, Norton et al 2012, Millen et al 2014, Libhaber et al 2014, Booysen et al 2015, Peterson et al 2016, Bamaiyi et al 2019). Left ventricular dimensions were determined using two-dimensional directed M-mode echocardiography in the short axis view and these recordings were analyzed according to the American Society of Echocardiography convention (Sahn et al 1978). Left ventricular mass was determined using a standard formula (Devereux et al 1976) and indexed (LVMI) to body surface area. Left ventricular diastolic function was determined from a pulsed wave Doppler examination of the mitral inflow at rest (early [E] and late [atrial contraction-A] velocity) and using tissue Doppler indices (TDI)(early [e'] and late [atrial contraction a'] velocity) as well as left atrial volumes (LAV) (Millen et al 2014, Peterson et al 2016, Bamaiyi et al 2019). Data were expressed as E/A, e'/a' and the E/e' ratio (an index of LV filling pressures). Left atrial volume was indexed to body surface area. Individuals were identified as having DD as described (Bamaiyi et al 2019) using criteria in-part recently advocated by guidelines (Nagueh et al 2016) as well as using criteria previously employed (Redfield et al 2003).

*2.3.6 Data analysis*

For database management and statistical analysis, SAS software, version 9.4 (SAS Institute Inc., Cary, NC) was employed. Continuous variables are expressed as mean (±SD).

Dichotomous variables are expressed as percentages. Relationships were evaluated from multivariate linear (continuous analysis) or logistic (discrete analysis) regression analysis. 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 determine the yearly contribution of the various loading conditions to LV structure and function, multivariate adjusted product of coefficient mediation analysis was performed. In both regression analysis and in mediation analysis, adjustments were in the first instance for age (except when age-related effects were assessed), sex, regular alcohol intake, regular tobacco intake, BMI, diabetes mellitus and/or an $HbA_{1c}$>6.5% and heart rate (for e', E/A and e'/a'). Adjustments were for factors correlated with age or measures of diastolic function in bivariate analysis. As LVMI may mediate a proportion of the effects of afterload on LV diastolic function, in secondary analysis associating either age or determinants of afterload with LV diastolic function, additional adjustments were for LVMI. Relationships were compared using z-statistics. As the impact of compression wave pressures depends on age, analysis was conducted in those either less than or more than 50 years of age (the age at which the compression wave begins to increase as identified from the inflection points of age-pressure wave relations [LOESS procedures in SAS software]). As more women than men volunteered for the present study sensitivity analysis was conducted in sex-specific groups. As antihypertensive therapy may influence the results, sensitivity analysis was also performed in those not receiving therapy.

## 2.4 Results

### *2.4.1 Participant characteristics*.

Table 2.1 shows the characteristics of the study sample. In general, a high proportion of participants had hypertension and obesity. Apart from modest differences in the proportion who were male, the age and the proportion treated for hypertension, participants without high quality aortic velocity measurements in the outflow tract showed similar characteristics as those with these measures (Table 2.2). Moreover, the prevalence of DD was similar in participants with and without high quality aortic velocity measurements in the outflow tract

Table 2.1. Participant characteristics.

| | |
|---|---|
| n (% male) | 605 (30.3) |
| Age (years) | 47.3±17.8 |
| Body mass index (kg/m$^2$) | 30.1±7.9 |
| % Overweight/obese | 23.8/46.8 |
| % Hypertensive | 48.7 |
| % Hypertensive confirmed with ABPM | 41.4 |
| % Uncontrolled hypertension* | 35.9 |
| % Treated for hypertension | 29.4 |
| % Diabetes mellitus (DM) | 13.1 |
| % Regular smokers | 16.2 |
| % Regular alcohol intake | 19.2 |
| SBP/DBP (mm Hg) | 128±22/82±13 |
| Pulse pressure (mm Hg) | 45±16 |
| Aortic pulse pressure (mm Hg) | 35±15 |
| SVR (mm Hg.min/l) | 22.2±9.9 |
| Backward wave pressure (Pb) (mm Hg) | 13±6 |
| Zc (dynes.s/cm$^5$) | 85±44 |
| Peak aortic flow (peak Q) (mls/sec) | 351±176 |
| Maximal $P_{Q \times Zc}$ (mm Hg) | 25±9 |
| <u>Left ventricular and atrial structure and function</u> | |
| Lateral wall e' (cm/sec) | 11.4±4.2 |
| Septal wall e' (cm/sec) | 9.6±3.7 |
| E/A | 1.27±0.52 |
| e'/a' | 1.50±0.82 |
| E/e' | 7.50±4.26 |
| Left atrial volume (LAV) index (ml/m$^2$) | 19.6±7.8 |
| LVM index (LVMI)(g/m$^2$) | 77.0±24.7 |
| Diastolic dysfunction (DD$^{\dagger}$)(%) | 15.2 |
| Diastolic dysfunction (DD$^{\ddagger}$)(%) | 27.8 |
| Left ventricular hypertrophy (%) | 16.4 |

Data are shown as mean±SD or proportions. *Refers to treated and untreated participants diagnosed with hypertension that had uncontrolled BP values. ABPM, 24-hour ambulatory BP monitoring; SVR, systemic vascular resistance; Zc, proximal aortic characteristic

impedance; Maximal $P_{Q \times Zc}$ , early systolic pulsatile load (pressures generated by the product of Zc and peak aortic flow); E/A, transmitral early/atrial blood flow velocity; e', myocardial tissue lengthening in early diastole at the mitral annulus; a', myocardial tissue lengthening in late diastole at the mitral annulus; E/e', transmitral early blood flow velocity/velocity of the mean value of lateral and septal wall myocardial tissue lengthening in early diastole at the mitral annulus; LVM, left ventricular mass; DD†, DD based on Nagueh et al 2016 but excluding pulmonary artery pressures; DD‡, DD based on reference Redfield et al 2003 but excluding Valsalva effects.

Table 2.2. Characteristics of participants without high quality velocity measurements in the outflow tract.

| Characteristic | | p-values vs those with (Table 1) |
|---|---|---|
| n (% male) | 440 (36.8) | (<0.05) |
| Age (years) | 43.9±18.4 | <0.005 |
| Body mass index (kg/m$^2$) | 29.2±7.5 | |
| % Overweight/obese | 23.0/43.0 | |
| % Hypertensive | 49.4 | |
| % Uncontrolled hypertension | 38.7 | |
| % Treated for hypertension | 23.6 | <0.05 |
| % Diabetes mellitus (DM) | 13.4 | |
| % Regular smokers | 13.4 | |
| % Regular alcohol intake | 21.4 | |
| SBP/DBP (mm Hg) | 130±22/83±12 | |
| Pulse pressure (mm Hg) | 46±15 | |

Data are shown as mean±SD or proportions.

(Table 2.3). A significant proportion of hypertensives had uncontrolled BP values despite a number of these individuals receiving antihypertensive medication. Based on current guidelines, 15.2% of the participants had DD and this was largely determined by a combination of either reductions in lateral or septal wall e' and increases in E/e' (73.9%). Based on previous criteria, 27.8% of the participants had DD and this was largely determined by mild (13.7%) or moderate (10.9%) DD. No participants had an ejection fraction<40% and 4.5% had an ejection fraction<50%. Of the sample 16.4% had LVH (LVMI>115 g/m$^2$ for men and >95 g/m$^2$ for women).

*2.4.2 Relationships between age and load.*

Systemic vascular resistance tended to show an inverse relationship with age across the full adult lifespan (Figure 2.1). However, striking and consistent incremental age-related increases in late systolic load (reflected waves, Pb) were nevertheless noted across the full adult lifespan (Figure 2.1). In contrast, peak $P_{QxZc}$ and brachial PP were positively related with age from 50 years of age until late adult life, but showed no relationships with age below 50 years of age (Figure 2.1).

*2.4.3 Relationships between age and LVMI and diastolic function and the hemodynamic determinants thereof.*

Inverse relationships between age and left ventricular E/A and e'/a' occurred across the full adult age range (Figure 2.2). These relations were unaffected by adjustments for LVMI (Figure 2.2). These changes were only modestly associated with increases in Pb (e'/a' above 50 years of age) with no independent inverse associations noted with SVR or peak $P_{QxZc}$ (Tables 2.4, 2.5 and 2.6). Striking inverse relationships between age and LV lateral and septal wall e' also occurred across the full adult lifespan (Figure 2.3) and in parallel with positive (direct) relationships noted between age and late systolic pulsatile load (reflected wave pressures, Pb) (Figure 2.1). Moreover, striking positive relationships between age and LVMI and LV filling pressures (E/e') occurred across the full adult lifespan, also in parallel with relationships between age and Pb (Figure 2.3). Further adjustments for LVMI only modestly influenced relations between age and LV diastolic function (Figure 2.3).

Table 2.3. Characteristics of participants without high quality velocity measurements in the outflow tract but with tissue Doppler assessments of diastolic function

| Characteristic | | p-values vs those with (Table 1) |
|---|---|---|
| n (% male) | 104 (40.0) | (=0.052) |
| Age (years) | 46.3±19.6 | |
| Body mass index (kg/m$^2$) | 29.9±8.0 | |
| % Overweight/obese | 18.3/45.8 | |
| % Hypertensive | 54.2 | |
| % Uncontrolled hypertension | 38.9 | |
| % Treated for hypertension | 29.2 | |
| % Diabetes mellitus (DM) | 13.3 | |
| % Regular smokers | 15.8 | |
| % Regular alcohol intake | 20.8 | |
| SBP/DBP (mm Hg) | 128±22/84±13 | |
| Pulse pressure (mm Hg) | 44.6±16.0 | |
| Aortic pulse pressure (mm Hg) | 35.2±14.7 | |
| Left ventricular and atrial structure and function | | |
| Lateral wall e' (cm/sec) | 10.7±3.6 | |
| Septal wall e' (cm/sec) | 9.4±3.4 | |
| E/A | 1.28±0.52 | |
| e'/a' | 1.47±0.80 | |
| E/e' | 7.52±4.03 | |
| Left atrial volume (LAV) index (ml/m$^2$) | 19.8±6.0 | |
| LVM index (LVMI)(g/m$^2$) | 78.9±24.8 | |
| Diastolic dysfunction (DD[a])(%) | 15.8 | |
| Diastolic dysfunction (DD[b])(%) | 28.3 | |
| Left ventricular hypertrophy (%) | 16.1 | |

Data are shown as mean±SD or proportions. See table 1 for abbreviations.

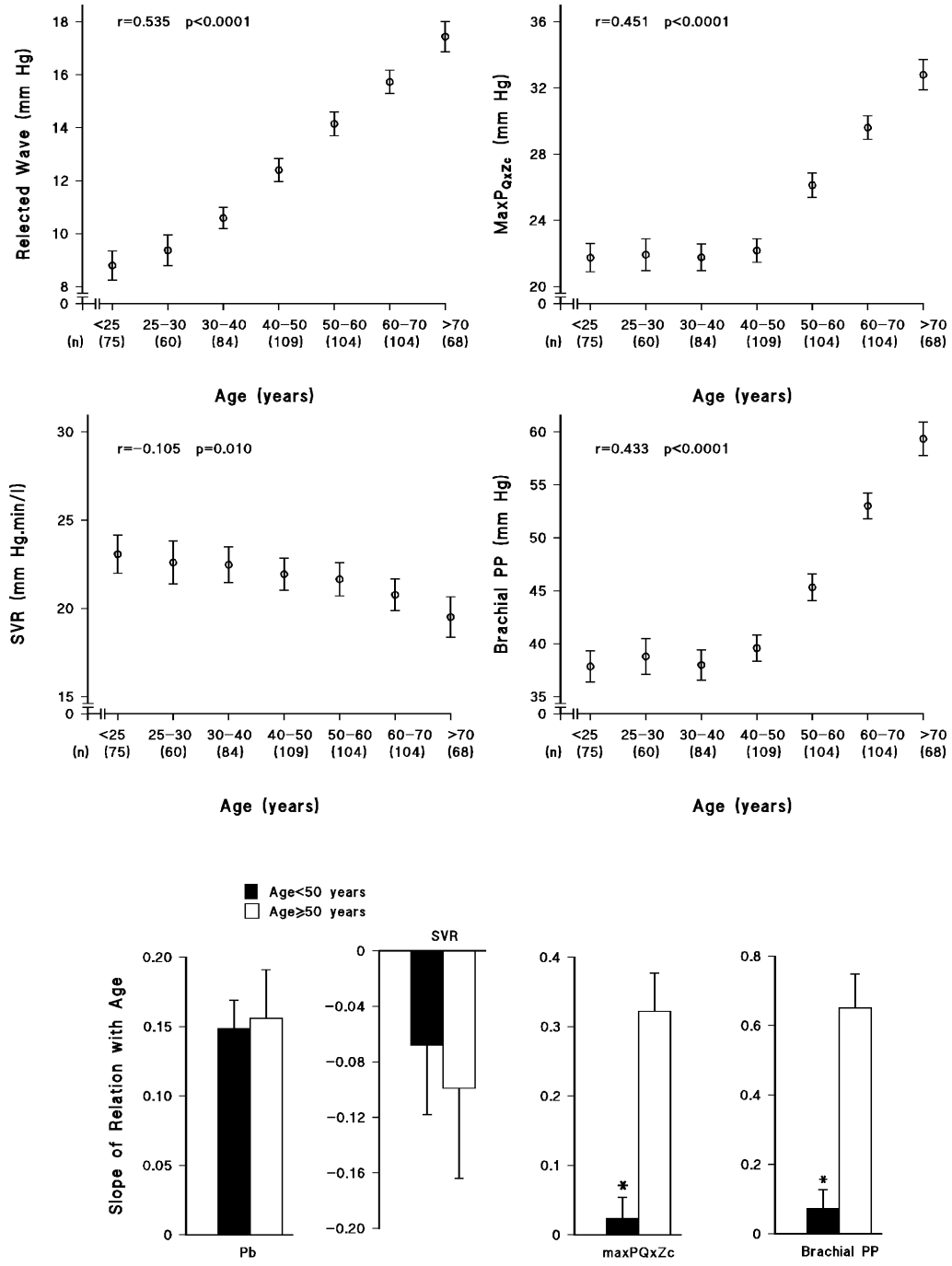


Figure 2.1. Relationships between age and systemic vascular resistance (SVR), brachial pulse pressure (PP), early systolic pulsatile load as indexed by the product of characteristic impedance [Zc] and peak aortic flow [Q], $P_{QxZc}$) and late systolic pulsatile load as determined by backward wave (reflected wave) pressures (Pb) across the full adult age range. Relationships between age and load are given in the whole group and for age groups below and above 50 years of age.

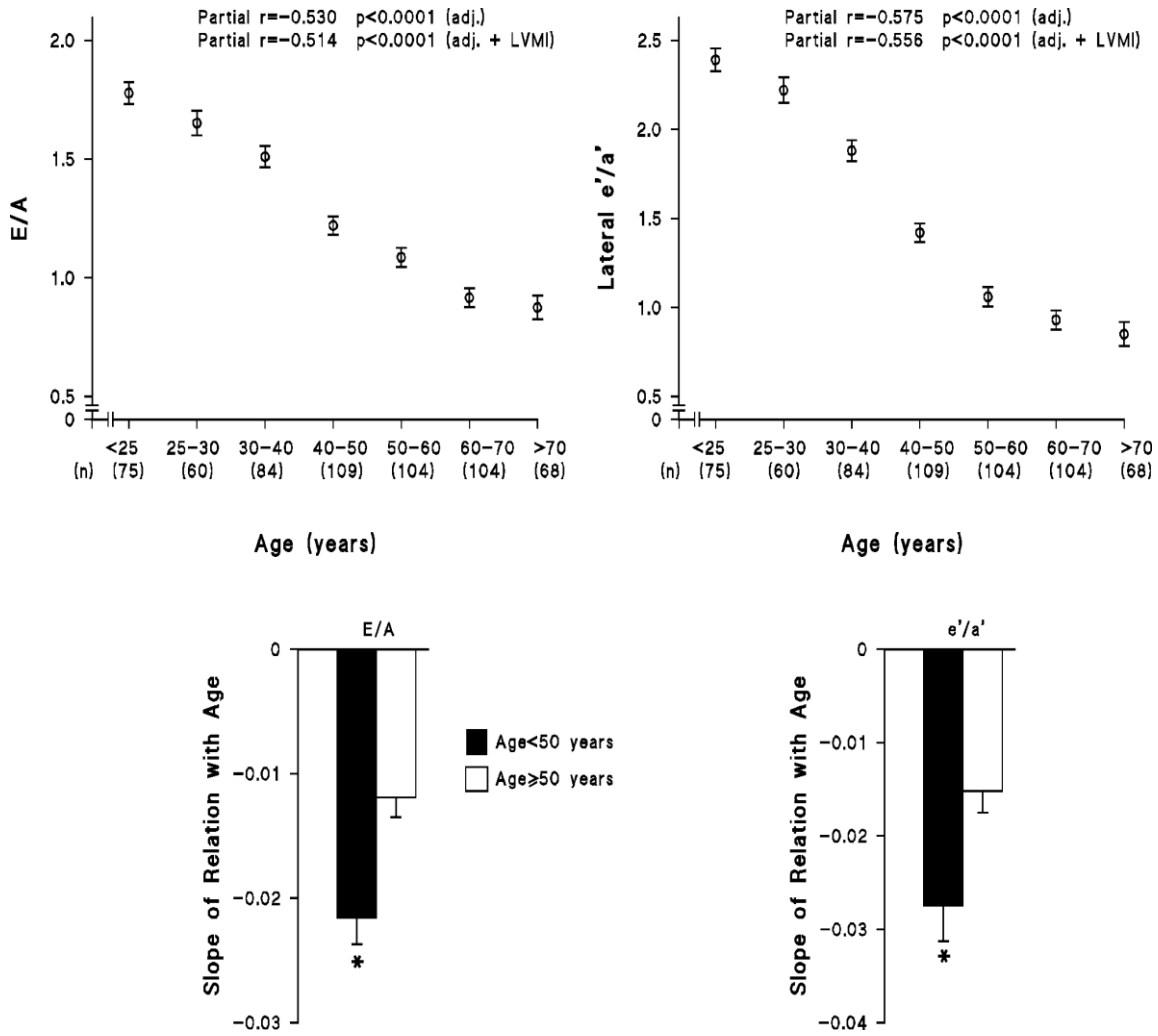


Figure 2.2. Multivariate adjusted indexes of left ventricular (LV) diastolic function across the full adult age range and multivariate adjusted slopes of relationships between age and LV function. Adjustments are for variations in body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5%, and heart rate. Partial r values shown for age-LV diastolic function relations are before and after additional adjustments for LVMI. Relationships between hemodynamic correlates and diastolic function in age-specific categories are shown in Table 2.4. See table 2.1 for abbreviations.

Table 2.4 Relationships (partial r) of various indexes of systemic load to variations in indexes of left ventricular (LV) diastolic function or LV mass index (LVMI) at different age ranges across the adult lifespan.

| | SVR | $P_{QxZc}$ | Pb |
|---|---|---|---|
| LV index | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
| | <50 years of age (n=328) | | |
| Lateral e' | -0.048 (-0.160 to 0.064) | 0.062 (-0.051 to 0.173) | -0.141 (-0.249 to -0.029)* |
| Septal e' | -0.074 (-0.184 to 0.037) | 0.036 (-0.076 to 0.146) | -0.119 (-0.226 to -0.009)* |
| E/A | 0.116 (0.004 to 0.224)* | 0.004 (-0.107 to 0.116) | 0.012 (-0.100 to 0.124) |
| e'/a' | 0.120 (0.008 to 0.228)* | 0.090 (-0.022 to 0.200) | -0.105 (-0.214 to 0.007) |
| E/e' | -0.037 (-0.149 to 0.075) | -0.064 (-0.175 to 0.048) | 0.181 (0.070 to 0.287)** |
| LAV index | -0.094 (-0.204 to 0.019) | 0.063 (-0.049 to 0.174) | -0.050 (-0.161 to 0.063) |
| LVMI | -0.202 (-0.305 to -0.093)** | -0.046 (-0.156 to 0.065) | 0.175 (0.066 to 0.280)** |
| | ≥50 years of age (n=277) | | |
| Lateral e' | -0.044 (-0.080 to 0.166) | 0.198 (0.076 to 0.314)** | -0.217 (-0.332 to -0.096)** |
| Septal e' | -0.053 (-0.174 to 0.069) | 0.122 (0.001 to 0.239)* | -0.129 (-0.247 to -0.008)* |
| E/A | 0.126 (0.002 to 0.246)* | 0.002 (-0.122 to 0.126) | -0.070 (-0.192 to 0.055) |
| e'/a' | 0.169 (0.049 to 0.285)* | 0.053 (-0.069 to 0.174) | -0.129 (-0.247 to -0.007)* |
| E/e' | -0.062 (-0.185 to 0.062) | -0.102 (-0.223 to 0.022) | 0.210 (0.088 to 0.325)** |
| LAV index | -0.010 (-0.132 to 0.111) | 0.044 (-0.078 to 0.165) | 0.046 (-0.076 to 0.167) |
| LVMI | -0.321 (-0.425 to -0.208)*** | -0.020 (-0.140 to 0.101) | 0.161 (0.040 to 0.276)* |

For abbreviations see table 1. SVR, $P_{QxZc}$, and Pb are included in the same regression models. Also included in the models are age, sex, body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate (for e', E/A and e'/a'). *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships.

Table 2.5**.** Relationships (partial r) of various indexes of systemic load to variations in indexes of left ventricular (LV) diastolic function or LV mass index (LVMI) at different age ranges across the adult lifespan in those not receiving antihypertensive therapy.

| | SVR | $P_{QxZc}$ | Pb |
|---|---|---|---|
| LV Index | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
| | <50 years of age (n=296) | | |
| Lateral e' | -0.081 (-0.195 to 0.036) | 0.087 (-0.030 to 0.201) | -0.180 (-0.290 to -0.065)** |
| Septal e' | -0.079 (-0.194 to 0.038) | 0.070 (-0.047 to 0.185) | -0.135 (-0.247 to -0.019)* |
| E/A | 0.115 (-0.003 to 0.231) | -0.009 (-0.126 to 0.109) | 0.025 (-0.092 to 0.143) |
| e'/a' | 0.118 (0.001 to 0.233)* | 0.072 (-0.046 to 0.188) | -0.101 (-0.216 to 0.017) |
| E/e' | 0.017 (-0.099 to 0.133) | -0.053 (-0.168 to 0.064) | 0.233 (0.120 to 0.340)*** |
| LAV index | -0.097 (-0.213 to 0.022) | 0.047 (-0.072 to 0.164) | -0.027 (-0.145 to 0.092) |
| LVMI | -0.215 (-0.323 to -0.101)** | -0.058 (-0.173 to 0.058) | 0.164 (0.049 to 0.275)* |
| | ≥50 years of age (n=131) | | |
| Lateral e' | 0.092 (-0.091 to 0.269) | 0.208 (0.026 to 0.374)* | -0.229 (-0.393 to -0.049)* |
| Septal e' | 0.063 (-0.120 to 0.241) | 0.097 (-0.086 to 0.274) | -0.193 (-0.361 to -0.011)* |
| E/A | 0.143 (-0.043 to 0.318) | -0.127 (-0.301 to 0.055) | -0.033 (-0.215 to 0.151) |
| e'/a' | 0.167 (-0.014 to 0.336) | -0.063 (-0.239 to 0.118) | -0.092 (-0.267 to 0.089) |
| E/e' | -0.140 (-0.310 to 0.040) | -0.157 (-0.328 to 0.026) | 0.215 (0.035 to 0.379)* |
| LAV index | 0.022 (-0.158 to 0.200) | 0.004 (-0.175 to 0.183) | 0.109 (-0.075 to 0.286) |
| LVMI | -0.360 (-0.505 to -0.191)*** | 0.007 (-0.173 to 0.185) | 0.240 (0.062 to 0.401)* |

For abbreviations see table 1. SVR, $P_{QxZc}$, and Pb are included in the same regression models. Also included in the models are age, sex, body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate (for e', E/A and e'/a'). *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships.

Table 2.6**.** Relationships (partial r) of various indexes of systemic load to variations in indexes of left ventricular (LV) diastolic function or LV mass index (LVMI) in sex-specific groups.

| | SVR | $P_{QxZc}$ | Pb |
|---|---|---|---|
| LV Index | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
| | Women (n=422) | | |
| Lateral e' | 0.019 (-0.077 to 0.116) | 0.154 (0.058 to 0.246)** | -0.186 (-0.277 to -0.091)*** |
| Septal e' | -0.077 (-0.173 to 0.019) | 0.079 (-0.018 to 0.175) | -0.110 (-0.205 to -0.013)* |
| E/A | 0.112 (0.015 to 0.207)* | 0.033 (-0.064 to 0.130) | -0.038 (-0.134 to 0.060) |
| e'/a' | 0.130 (0.033 to 0.224)* | 0.150 (0.053 to 0.244)** | -0.157 (-0.250 to 0.061)** |
| E/e' | -0.023 (-0.121 to 0.076) | -0.137 (-0.232 to -0.039)* | 0.257 (0.163 to 0.347)*** |
| LAV index | -0.073 (-0.170 to 0.026) | 0.090 (-0.008 to 0.188) | -0.010 (-0.108 to 0.088) |
| LVMI | -0.250 (-0.339 to -0.157)*** | 0.002 (-0.095 to 0.099) | 0.117 (0.020 to 0.211)* |
| | Men (n=183) | | |
| Lateral e' | -0.023 (-0.171 to 0.127) | 0.067 (-0.083 to 0.214) | -0.182 (-0.322 to -0.033)* |
| Septal e' | -0.028 (-0.176 to 0.121) | 0.031 (-0.118 to 0.179) | -0.157 (-0.300 to -0.007)* |
| E/A | -0.067 (-0.216 to 0.085) | 0.068 (-0.082 to 0.215) | -0.129 (-0.273 to 0.020) |
| e'/a' | 0.145 (-0.008 to 0.291) | 0.073 (-0.078 to 0.221) | -0.095 (-0.240 to 0.055) |
| E/e' | -0.024 (-0.174 to 0.126) | -0.003 (-0.153 to 0.147) | 0.206 (0.056 to 0.345)* |
| LAV index | -0.051 (-0.201 to 0.100) | 0.029 (-0.122 to 0.179) | 0.006 (-0.145 to 0.157) |
| LVMI | -0.354 (-0.477 to -0.214)*** | 0.005 (-0.144 to 0.154) | 0.153 (0.004 to 0.294)* |

For abbreviations see table 1. SVR, $P_{QxZc}$, and Pb are included in the same regression models. Also included in the models are age, body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate (for e', E/A and e'/a'). *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships.

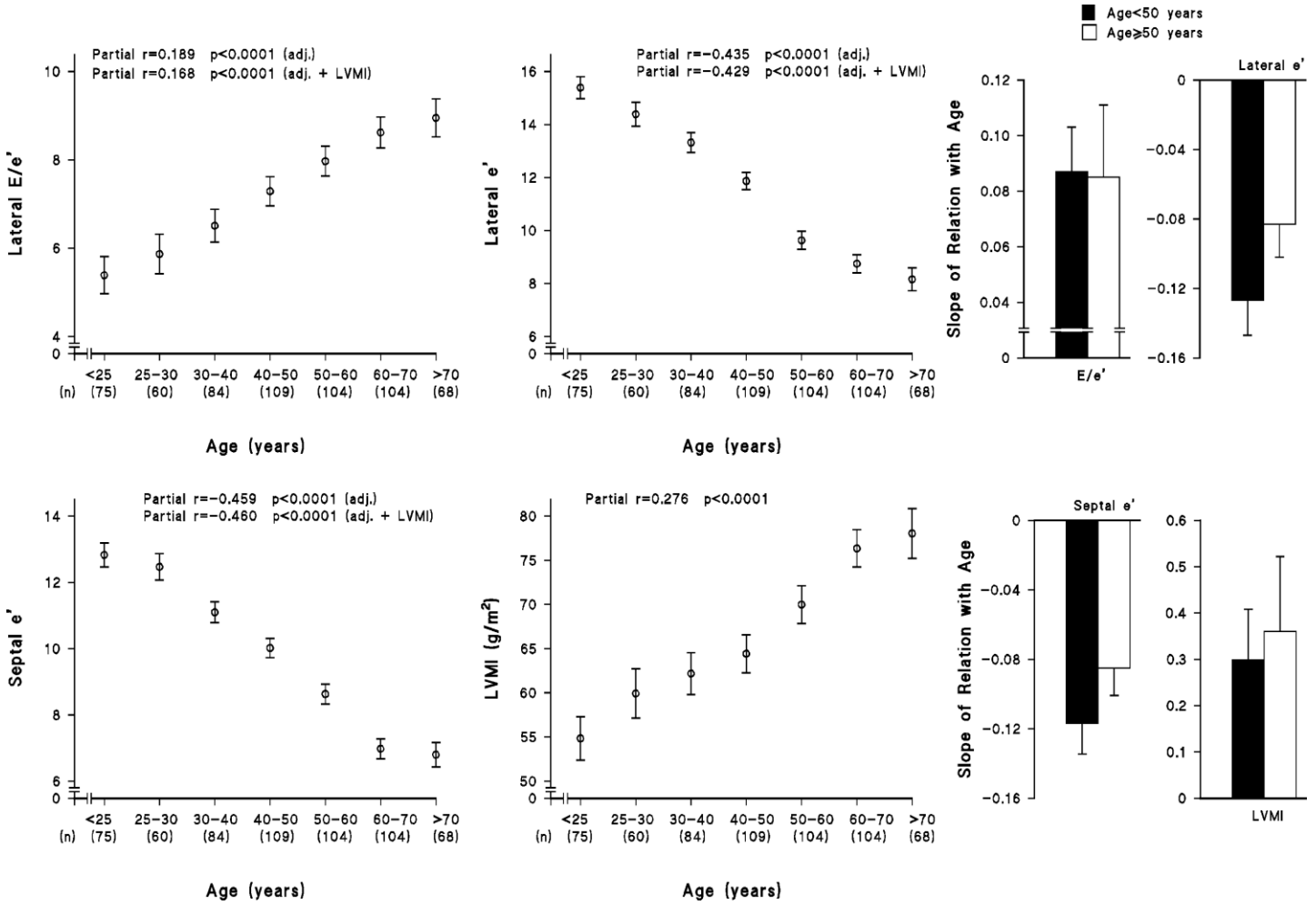


Figure 2.3. Multivariate adjusted relationships between age and indexes of left ventricular (LV) mass index (LVMI) and diastolic function across the full adult age range and multivariate adjusted relationships between age and LVMI and function. Adjustments are for variations in body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate (for e'). Partial r values shown for age-

LV diastolic function relations are before and after additional adjustments for LVMI. Relationships between hemodynamic correlates and LVMI or diastolic function in age-specific categories are shown in Table 2. See table 1 for abbreviations.

Without hemodynamic factors included in the regression models, age showed by far the strongest impact in relations with LVMI or LV E/e' or e' (Table 2.7). Of importance the impact of age on LV diastolic function (β-coefficient) was as marked in the younger adult age range (<50 years of age) as compared to the older age range (Figure 2.3).

In multivariate models with SVR together with indexes of pulsatile load, late systolic pulsatile load (Pb), but not early systolic pulsatile load (peak $P_{QxZc}$), or SVR was positively and independently associated with LVMI, LVH, and E/e' and negatively and independently associated with lateral and septal wall e' both before and after 50 years of age (Tables 2.4, 2.5 and 2.6). After 50 years of age, with Pb in the regression model, because the impact of compression wave pressures is mediated by Pb, peak $P_{QxZc}$ showed inverse relations with indexes of LV diastolic function (Tables 2.4, 2.5 and 2.6). The impact of Pb in relations with LVMI and LV diastolic function was similar in direction to that of peak aortic PP or SBP (Table 2.8). Similar relations were noted between compression (peak $P_{QxZc}$) or backward wave pressures and LVMI or LV diastolic function when adjusting for steady-state pressures (MAP) (Table 2.9). In this regard, while Pb showed independent relations beyond peak $P_{QxZc}$ and MAP, peak $P_{QxZc}$ showed no independent relations beyond Pb and MAP at either a younger or an older adult age (Table 2.9). Importantly, relations between Pb and e' or E/e' were independent of brachial SBP (Table 2.10) and PP (data not shown). LAVI was not independently associated with either SVR or pulsatile load (Table 2.4).

*2.4.4 Contribution of load to relationships between age and LV diastolic function*

Importantly, adjustments for Pb reduced the age-e' or E/e' relations (Figure 2,4) and this effect was similar in those below as above 50 years of age (Figure 2.4). While adjustments for Pb either abolished (age-E/e') or reduced (age-e') the significance of the relations, adjustments for brachial SBP or PP failed to impact on these relations (Figure 2.4). The impact of age on LV E/e' was almost completely eliminated with the inclusion of Pb in the regression models, and Pb then showed a dominant effect (Table 2.7). However, the striking impact of age on LV e' was only partly diminished with the inclusion of Pb in the regression models, with age retaining a dominant effect (Table 2.7).

Table 2.7**.** Relative impact of risk factors in relations with indexes of left ventricular mass index (LVMI) and diastolic function across the adult lifespan in a community sample (n=605).

| Models with backward wave pressures (Pb) → | Without | | With | |
|---|---|---|---|---|
| | β-coeff±SEM | p-value | β-coeff±SEM | p-value |
| Risk Factors | | | | |
| | | **LVMI** | | |
| Pb | - | - | 0.155±0.045 | =0.0006 |
| Age | 0.315±0.045 | <0.0001 | 0.235±0.050 | <0.0001 |
| Male sex | 0.183±0.042 | <0.0001 | 0.187±0.042 | <0.0001 |
| Regular smoking | 0.032±0.044 | =0.47 | 0.020±0.044 | =0.65 |
| Regular alcohol intake | 0.061±0.042 | =0.15 | 0.062±0.042 | =0.14 |
| Diabetes mellitus | 0.004±0.042 | =0.92 | 0.004±0.041 | =0.93 |
| | | **LV E/e'** | | |
| Pb | - | - | 0.250±0.045 | <0.0001 |
| Age | 0.215±0.046 | <0.0001 | 0.086±0.050 | =0.090 |
| Male sex | -0.062±0.045 | =0.17 | -0.057±0.044 | =0.19 |
| Regular smoking | 0.008±0.044 | =0.85 | 0.012±0.043 | =0.78 |
| Regular alcohol intake | 0.031±0.043 | =0.46 | 0.033±0.041 | =0.43 |
| Body mass index | 0.136±0.046 | =0.0032 | 0.132±0.045 | =0.0033 |
| Diabetes mellitus | 0.038±0.042 | =0.36 | 0.037±0.041 | =0.36 |
| | | **LV lateral wall e'** | | |
| Pb | - | - | -0.126±0.040 | =0.0019 |
| Age | -0.458±0.039 | <0.0001 | -0.388±0.045 | <0.0001 |
| Male sex | 0.067±0.039 | =0.090 | 0.077±0.039 | =0.048 |
| Regular smoking | 0.039±0.037 | =0.30 | 0.031±0.038 | =0.40 |
| Regular alcohol intake | 0.016±0.036 | =0.66 | 0.012±0.036 | =0.73 |
| Body mass index | -0.223±0.039 | <0.0001 | -0.221±0.039 | <0.0001 |
| Diabetes mellitus | -0.064±0.036 | =0.070 | -0.066±0.036 | =0.066 |
| Heart rate | -0.067±0.035 | =0.054 | -0.088±0.035 | =0.012 |

β-coeff, standardized β-coefficient.

Table 2.8**.** Relationships (partial r) of central aortic pulse pressure (PPc) or systolic blood pressure (SBPc) to variations in indexes of left ventricular (LV) diastolic function or LV mass index (LVMI) in a community sample.

| | PPc | | SBPc | |
|---|---|---|---|---|
| LV Index | Partial r (95% CI) | p-value | Partial r (95% CI) | p-value |
| Lateral e' | -0.080 (-0.159 to 0.001) | =0.054 | -0.173 (-0.250 to -0.093) | <0.0001 |
| Septal e' | -0.062 (-0.142 to 0.019) | =0.13 | -0.127 (-0.205 to -0.047) | =0.002 |
| E/A | -0.085 (-0.164 to -0.004) | =0.040 | -0.128 (-0.206 to -0.048) | =0.002 |
| e'/a' | -0.042 (-0.122 to 0.039) | =0.31 | -0.150 (-0.227 to -0.070) | =0.0002 |
| E/e' | 0.182 (0.103 to 0.259) | <0.0001 | 0.165 (0.085 to 0.242) | <0.0001 |
| LAV index | 0.083 (0.001 to 0.163) | =0.047 | 0.084 (0.002 to 0.164) | =0.045 |
| LVMI | 0.179 (0.100 to 0.255) | <0.0001 | 0.213 (0.135 to 0.289) | <0.0001 |

For abbreviations see table 1. Adjustments are for age, body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate (for e', E/A and e'/a').

Table 2.9**.** Steady-state pressure (MAP)-independent relationships (partial r) of indexes of pulsatile load with variations in indexes of left ventricular (LV) diastolic function or LV mass index (LVMI) at different age ranges across the adult lifespan.

| | $P_{QxZc}$ | | Pb | |
|---|---|---|---|---|
| LV Index | Partial r (95% CI) | p-value | Partial r (95% CI) | p-value |
| | <50 years of age (n=328) | | | |
| Lateral e' | 0.092 (-0.018 to 0.199) | =0.10 | -0.137 (-0.242 to -0.027) | =0.014 |
| Septal e' | 0.046 (-0.065 to 0.156) | =0.42 | -0.119 (-0.226 to -0.008) | =0.035 |
| E/A | 0.025 (-0.087 to 0.137) | =0.66 | 0.007 (-0.105 to 0.119) | =0.89 |
| e'/a' | 0.088 (-0.024 to 0.199) | =0.12 | -0.076 (-0.187 to 0.037) | =0.18 |
| E/e' | -0.052 (-0.161 to 0.059) | =0.36 | 0.188 (0.079 to 0.292) | =0.0007 |
| LAV index | 0.077 (-0.036 to 0.188) | =0.18 | -0.069 (-0.180 to 0.044) | =0.23 |
| LVMI | -0.028 (-0.139 to 0.083) | =0.61 | 0.115 (0.004 to 0.223) | =0.043 |
| | ≥50 years of age (n=277) | | | |
| Lateral e' | 0.193 (0.074 to 0.306) | =0.0016 | -0.216 (-0.328 to -0.096) | =0.0004 |
| Septal e' | 0.158 (0.035 to 0.276) | =0.012 | -0.108 (-0.229 to 0.016) | =0.086 |
| E/A | 0.066 (-0.058 to 0.189) | =0.29 | -0.103 (-0.224 to 0.022) | =0.104 |
| e'/a' | 0.045 (-0.077 to 0.166) | =0.47 | -0.150 (-0.267 to -0.029) | =0.015 |
| E/e' | -0.081 (-0.199 to 0.039) | =0.19 | 0.181 (0.061 to 0.295) | =0.0032 |
| LAV index | 0.039 (-0.083 to 0.160) | =0.53 | 0.015 (-0.107 to 0.137) | =0.81 |
| LVMI | 0.010 (-0.112 to 0.133) | =0.87 | 0.095 (-0.028 to 0.215) | =0.13 |

For abbreviations see table 1. MAP, $P_{QxZc}$, and Pb are included in the same regression models. Also included in the models are age, sex, body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate (for e', E/A and e'/a').

Table 2.10**.** Brachial systolic pressure-independent relations between various indexes of systemic load and indexes of left ventricular (LV) diastolic function or mass index (LVMI) at different age ranges across the adult lifespan.

| | SVR | $P_{QxZc}$ | Pb |
|---|---|---|---|
| LV Index | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
| | <50 years of age (n=328) | | |
| Lateral e' | -0.010 (-0.120 to 0.100) | 0.100 (-0.011 to 0.208) | -0.119 (-0.226 to -0.008)* |
| Septal e' | -0.063 (-0.172 to 0.049) | 0.044 (-0.067 to 0.154) | -0.110 (-0.218 to 0.00)* |
| E/A | 0.147 (0.036 to 0.255)* | 0.045 (-0.067 to 0.157) | 0.050 (-0.062 to 0.161) |
| e'/a' | 0.166 (0.054 to 0.273)** | 0.146 (0.034 to 0.254)* | -0.051 (-0.162 to 0.061) |
| E/e' | -0.014 (-0.124 to 0.096) | -0.095 (-0.204 to 0.015) | 0.176 (0.066 to 0.281)** |
| LAV index | -0.095 (-0.205 to 0.018) | 0.056 (-0.057 to 0.167) | -0.053 (-0.164 to 0.060) |
| LVMI | -0.262 (-0.362 to -0.156)*** | -0.117 (-0.225 to -0.006)* | 0.120 (0.009 to 0.228)* |
| | ≥50 years of age (n=277) | | |
| Lateral e' | 0.092 (-0.030 to 0.211) | 0.240 (0.122 to 0.350)*** | -0.186 (-0.301 to -0.066)** |
| Septal e' | -0.024 (-0.146 to 0.098) | 0.158 (0.036 to 0.275)* | -0.122 (-0.241 to 0.00)* |
| E/A | 0.158 (0.034 to 0.276)* | 0.061 (-0.064 to 0.184) | -0.046 (-0.169 to 0.079) |
| e'/a' | 0.199 (0.078 to 0.313)** | 0.113 (-0.010 to 0.231) | -0.102 (-0.221 to 0.020) |
| E/e' | -0.070 (-0.189 to 0.051) | -0.102 (-0.219 to 0.019) | 0.201 (0.082 to 0.314)** |
| LAV index | -0.029 (-0.150 to 0.094) | 0.002 (-0.120 to 0.124) | 0.027 (-0.095 to 0.149) |
| LVMI | -0.364 (-0.464 to -0.253)*** | -0.118 (-0.235 to 0.004) | 0.125 (0.003 to 0.243)* |

For abbreviations see table 2.1. SVR, $P_{QxZc}$, and Pb are included in the same regression models. Also included in the models are brachial systolic blood pressure, age, sex, body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate (for e', E/A and e'/a'). *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships.

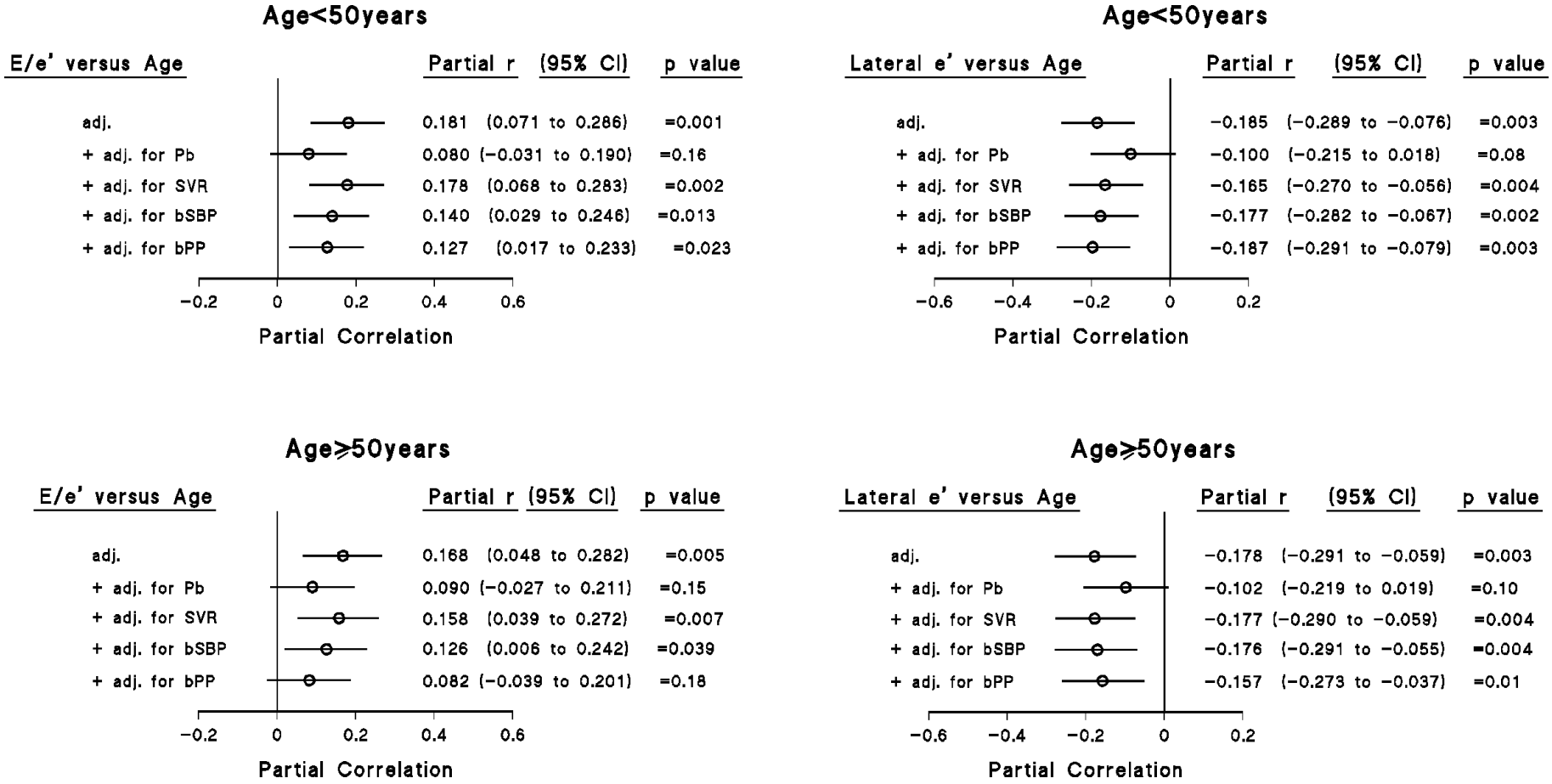


Figure 2.4. Impact of adjustments for hemodynamic factors on age relations (partial r values) with diastolic function in participants younger or older than 50 years of age in a community sample. Adjustments are for variations in hemodynamic factors as indicated and body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate (for e'). See table 2.1 for abbreviations.

In product of coefficient mediation analysis, the relationships between age and indexes of LV diastolic function were in-part accounted for by relationships between age and late systolic pulsatile load (Pb), but not SVR and the impact of Pb was similar before as after 50 years of age (Figure 2.5). In contrast neither brachial SBP nor PP accounted for as much of the impact of age on LV diastolic function as Pb (Figure 2.5).

*2.4.5 Independent associations between load and LV diastolic dysfunction (DD).*

A high proportion of individuals had DD with most DD occurring in those over 50 years of age (Table 2.11). Independent of confounders in participants either less than or more than 50 years of age, late (Pb), but not early (compression wave, peak $P_{QxZc}$) systolic pulsatile load or SVR were independently associated with LV DD (Table 2.11). These relations between Pb and LV DD were independent of brachial artery SBP (Table 2.11) or PP (data not shown). Peak aortic PP or SBP failed to show independent relations with DD (Table 2.12).

## 2.5 Discussion

The main findings of the present study are as follows: In a community with a high prevalence of hypertension, LVH and DD, we evaluated the impact of variable loading conditions on LV structure and function across the full adult age range. We note that marked relationships between age and LV diastolic function occur across the full adult lifespan. Moreover, despite the variable loading conditions that occur at different ages, the load that contributes most to the relationship between age and LV diastolic function is that produced by the impact of late systolic pulsatile load (backward wave pressures) starting at an early adult age and continuing to an advanced adult age. In this regard, we show first that the relationships between age and LV diastolic function are as marked in the early adult years as they are later in adult life.

Second, in mediation analysis we show that the dominant load that accounts for these effects is an enhanced reflected (backward) wave pressure which increases from an early adult age and accounts for a significant portion of the gradual linear increase in filling pressures (increased E/e') and decrease in myocardial relaxation (LV wall e') noted with

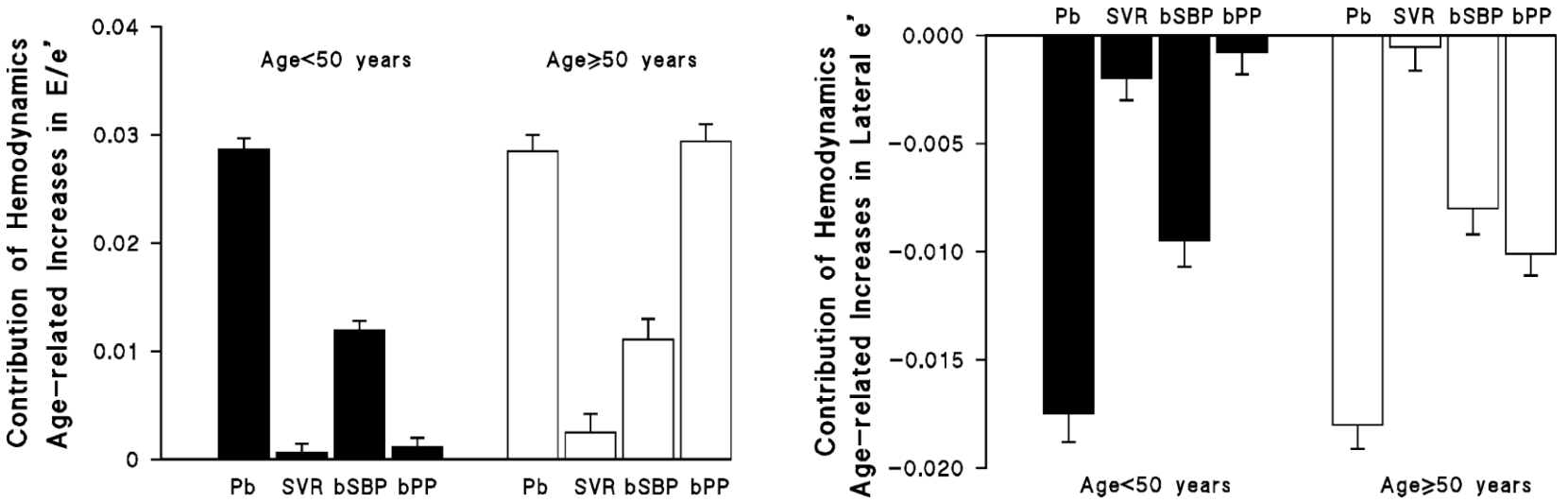


Figure 2.5. Multivariate adjusted contribution (product of coefficient mediation analysis) of hemodynamic correlates to relationships between age and diastolic function (expressed as change in diastolic functional parameter per year of age) in participants younger or older than 50 years of age. Adjustments are for variations in alternative hemodynamic factors and body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate (for e'). See table 2.1 for abbreviations.

Table 2.11**.** Relationship of various indexes of systemic load to the presence of left ventricular (LV) hypertrophy (LVH) or diastolic dysfunction (DD) at different age ranges across the adult lifespan.

| | | SVR | $P_{QxZc}$ | Pb |
|---|---|---|---|---|
| | Adjustments | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| LVH or DD versus | | | | |
| | | <50 years of age (n=328) | | |
| Left ventricular hypertrophy | | (n=24 of 328) | | |
| | * | 0.877 (0.802 to 0.959)[§§] | 1.039 (0.942 to 1.145) | 1.165 (1.012 to 1.340)[§] |
| | * + SBP | 0.880 (0.804 to 0.962)[§§] | 1.049 (0.940 to 1.171) | 1.178 (1.012 to 1.371)[§] |
| Diastolic dysfunction (newer criteria)[†] | | (n=17 of 328) | | |
| | * | 1.013 (0.963 to 1.064) | 1.009 (0.883 to 1.152) | 1.233 (1.014 to 1.500)[§] |
| | * + SBP | 0.990 (0.934 to 1.050) | 0.946 (0.818 to 1.093) | 1.254 (1.020 to 1.543)[§] |
| Diastolic dysfunction (older criteria)[‡] | | (n=43 of 328) | | |
| | * | 1.015 (0.982 to 1.049) | 0.988 (0.905 to 1.078) | 1.184 (1.035 to 1.354)[§] |
| | * + SBP | 1.001 (0.964 to 1.038) | 0.966 (0.882 to 1.057) | 1.164 (1.009 to 1.343)[§] |
| | | <50 years of age (n=277) | | |
| Left ventricular hypertrophy | | (n=75 of 277) | | |
| | * | 0.927 (0.888 to 0.967)[§§] | 0.980 (0.929 to 1.033) | 1.102 (1.015 to 1.196)[§] |
| | * + SBP | 0.907 (0.865 to 0.952)[§§] | 0.960 (0.905 to 1.019) | 1.100 (1.008 to 1.201)[§] |
| Diastolic dysfunction (newer criteria)[†] | | (n=75 of 277) | | |

| | | | | |
|---|---|---|---|---|
| | * | 0.984 (0.948 to 1.021) | 0.996 (0.944 to 1.051) | 1.102 (1.012 to 1.199)§ |
| | * + SBP | 0.980 (0.944 to 1.018) | 0.977 (0.921 to 1.036) | 1.097 (1.003 to 1.198)§ |
| Diastolic dysfunction (older criteria)‡ | | (n=125 of 277) | | |
| | * | 0.982 (0.949 to 1.015) | 0.989 (0.940 to 1.041) | 1.100 (1.013 to 1.194)§ |
| | * + SBP | 0.981 (0.949 to 1.015) | 0.987 (0.934 to 1.042) | 1.097 (1.008 to 1.194)§ |

For abbreviations see table 2.1. SVR, $P_{QxZc}$, and Pb are included in the same regression models. *Also included in the models are age, sex, body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5%, heart rate and brachial systolic blood pressures (SBP) as indicated. †, Diastolic dysfunction based on Nagueh et al 2016 but excluding pulmonary artery pressures; ‡, Diastolic dysfunction based on Redfield et al 2003 but excluding Valsalva effects. §p<0.05, §§p<0.005 for significance of relationship.

Table 2.12**.** Relationship of peak aortic blood pressures to the presence of left ventricular (LV) diastolic dysfunction (DD) at different age ranges across the adult lifespan.

| | <50 years of age | | ≥50 years of age | |
|---|---|---|---|---|
| | Odds ratios (95% CI) | | Odds ratios (95% CI) | |
| Adjustments | PPc | SBPc | PPc | SBPc |
| DD versus | | | | |
| Diastolic dysfunction (newer criteria)† | n=17 of 328 | | n=75 of 277 | |
| * | 1.012 (0.979 to 1.045) | 1.039 (0.983 to 1.100) | 1.011 (0.989 to 1.035) | 1.023 (0.988 to 1.060) |
| Diastolic dysfunction (older criteria)‡ | n=43 of 328 | | n=125 of 277 | |
| * | 1.006 (0.979 to 1.033) | 1.024 (0.973 to 1.077) | 1.006 (0.985 to 1.028) | 0.979 (0.947 to 1.013) |

PPc, central arterial pulse pressure; SBPc, central arterial systolic blood pressure. *Also included in the models are age, sex, mean arterial pressure, body mass index, regular smoking, regular alcohol intake, diabetes mellitus or an $HbA_{1c}$>6.5% and heart rate. †, Diastolic dysfunction based on Nagueh et al 2016 but excluding pulmonary artery pressures; ‡, Diastolic dysfunction based on Redfield et al 2003 but excluding Valsalva effects. No relations were significant.

aging. Of significance, the relations between backward wave pressures and indexes of LV diastolic function and the contribution of backward wave pressures to the relationship between age and LV diastolic function were as strong over the younger adult age (<50 years of age) as in those over 50 years of age and were well beyond brachial BP in both age ranges. Importantly, the impact of backward wave pressures on LV diastolic function in early adult life occurred despite the limited increase in PP that occurs over this period of life (Namasivayam et al 2009, Hodson et al 2017). The present study is the first to identify that progressive stepwise age-related decreases in LV diastolic function begin from a young adult age. Moreover, the present study is the first to show that the dominant load responsible for DD is initiated at a very early adult age, well before striking increases in brachial PP occur. In this regard, although SVR is an essential determinant of LV wall stress (Chirinos et al 2012), as indicated by the present study, SVR does not influence indexes of DD.

In contrast however, we show that increases in backward wave pressures starting in late teenage years and increasing incrementally across the full adult lifespan (Namasivayam et al 2009, Hodson et al 2017) explain a progressive age-related decrease in LV diastolic function. These data are consistent with several findings of a relationship between late systolic pulsatile LV load, mediated by wave reflection, and LV diastolic function (Weber et al 2006, Hashimoto et al 2006, Weber et al 2008, Ikonomidis et al 2008, Chirinos et al 2013, Peterson et al 2016). The present study nevertheless further adds to these findings (Weber et al 2006, Hashimoto et al 2006, Weber et al 2008, Ikonomidis et al 2008, Chirinos et al 2013, Peterson et al 2016) by demonstrating that these effects originate at a very early adult age and that the impact on diastolic function is as strong over this early period of life as it is later in life. In this regard, we show that the relationship between age and diastolic function was as marked over the early adult years as it is in later adult life. Importantly, the equivalence of the impact of Pb on LV diastolic function over early as compared to later adult life is despite the limited increase in brachial PP that occurs in early as compared to later adult life (Namasivayam et al 2009,

Hodson et al 2017). These effects were therefore consistently noted to be beyond brachial BP. These data suggest a gradual worsening of DD mediated in-part by increases in reflected wave pressures beginning at a young adult age and progressing to old age.

The results of the present study showing independent relations between backward wave pressures and e'/a' in the older age group, are consistent with previously described age-unadjusted associations between backward wave pressures and E/A (Sibiya et al 2015). However, present guidelines (Nagueh et al 2016) only recommend the use of indexes of ratios between early versus late diastolic filling in those with a reduced EF, and hence that finding (Sibiya et al 2015) conducted at a time when tissue Doppler indexes were not available to us, may have little clinical relevance. Subsequent work performed using tissue Doppler indexes, showed a similar relationship of both forward and backward pressure waves with tissue Doppler indexes of DD (Peterson et al 2016). However, the previously reported relations between forward wave pressures and LV diastolic function in the present population (Peterson et al 2016) are confounded by the impact of wave re-reflection produced by increases in late systolic load (backward wave pressure) (Phan et l 2016), and hence over-inflate the role of early systolic load. The use in the present study of the peak pressure generated by the product of Zc and Q as the measure of early systolic load therefore addresses this concern. In this regard, when included in the same regression models, the present study shows strong age-adjusted relations between backward wave pressures, but not the pressures generated by the product of Q and Zc and several indexes of LV diastolic function (E/e' and e') currently recommended for clinical use in the presence of a normal EF (all participants) (Nagueh et al 2016). Thus, the present study supports the importance of backward wave pressures as the major determinant of afterload responsible for DD at any age across the adult lifespan.

Although aortic stiffness is associated with DD or HFpEF (Hundley et al 2001, Kawaguchi et al 2003, Desai et al 2009, Kang et al 2010, Mohammed et al 2012, Coutinho et al 2013) and forward wave pressures with indexes of LV filling pressures (Peterson et al 2016),

the present study suggests that increases in aortic stiffness and consequently forward wave pressures may produce DD through an impact on backward wave pressures. Indeed, through inertial effects (Newton's Laws of Motion) increases in forward wave pressures enhance backward wave pressures (Nichols et al 2011). In keeping with this notion, in the present study we show that linear relationships between age and diastolic LV function occurred in parallel with age-related changes in reflected wave pressures, while pressure waves generated by the product of Q and Zc fail to show relations beyond reflected wave pressures. Importantly, the relations of LV diastolic function and reflected wave pressures begin before pressure waves generated by Zc increase with age. Nevertheless, LV diastolic function gradually worsens as pressure waves generated by increases in Zc enhance backward wave pressures at an older adult age.

Although speculative, the clinical implications of the present study are worthy of consideration. Whether the numerous cellular changes that account for increases in filling pressures and decreases in myocardial relaxation that contribute to DD and hence HFpEF can be reversed, is unknown. As there is presently no convincing evidence for beneficial effects of therapy in HFpEF, the chances of reversibility of DD are likely to be low. Thus, preventing the progression to DD may be an essential approach and as suggested by the present study LV diastolic function shows an age-related progressive deterioration starting at a young adult age. As relations between Pb and LV diastolic function are as strong over a younger (<50 years) as opposed to older adult age, the present study suggests that the impact of reflected waves on LV diastolic function is as striking over the early as opposed to the late adult years. Consequently, if wave reflection is increased over the younger adult age, by 50 years of age LV diastolic functional reserve may already be limited. Thus, targeting wave reflection from an early adult age may be an important goal in reducing the chances of progressing to DD at an older adult age. Brachial BP measurements are nevertheless unlikely to adequately identify the impact of reflected wave pressures on DD at any age.

At present there are no therapeutic approaches available that specifically decrease wave reflection. However, several studies, including major clinical trials (Tapp et al 2010) have demonstrated improvements in contemporary measures of LV diastolic function following antihypertensive therapy. In this regard, reductions in forward wave pressures through effects of therapy on MAP (distending pressures) will indirectly reduce reflected wave pressures (inertial effects of compression waves on reflected wave pressures) (Nichols et al 2011). Moreover, vasodilators may decrease wave reflection (Nichols et al 2011), but the extent to which this occurs beyond forward wave effects is uncertain. Importantly, the impact of these approaches on backward wave pressures at different times over the full adult age range, where wave reflection is determined by different factors (vascular tone either because of or beyond arteriolar function or forward wave effects) is unknown.

There are several limitations to the present study that warrant consideration. First, the present study was cross-sectional in design and explored relations with LV diastolic function and not with the development of HFpEF. Hence no conclusions regarding causality can be drawn and further longitudinal and outcome driven studies are required. However, these studies will require follow up from an early adult age to late in life and also a sufficiently large sample to capture a significant number of patients developing HFpEF. Second, in the present study pulmonary artery pressures were not included in the diagnosis of DD as at the time of initiating the study (2001) this measurement was not employed for routine assessment. As the diagnosis of DD in those with a normal EF (as in the present study) requires more than 2 of the 4 criteria to be present (Nagueh et al 2016), we may have included indeterminate participants as having DD. Nevertheless, current criteria for the diagnosis of DD have been developed for clinical samples in patients with a high suspicion of heart failure and not for community-based participants in whom there is little suspicion of heart failure. We nevertheless also showed similar relations with DD when employing the original criteria (Redfield et al 2003) proposed several years prior to recent guidelines (Nagueh et al 2016) and applied to a community setting.

However, using the previously described criteria for identifying DD (Redfield et al 2003), pseudo-normalisation of E/A was identified by determining changes noted with the Valsalva manoeuvre, an approach which we were unable to reproducibly perform. Nevertheless, moderate DD, which results in pseudo-normalisation of E/A may also be identified from E/e' >10 (Redfield et al 2003), an approach employed in the present study for the diagnosis of DD. Third, we determined SVR from SV derived from measurements in the outflow tract (product of velocity-time integral and aortic root cross-sectional area) rather than with more advanced approaches such as 3-dimensional cardiac magnetic resonance imaging. However, the approach employed in the present study is not limited by echocardiographic approaches that assume a uniform 3-dimensional LV geometry. Fourth, in the present study, calibration of the radial waveform from brachial BP measurements ignores amplification of BP from brachial to radial arteries (Picone et al 2015). Hence, aortic pressures may have been underestimated using the current approach. However, all central pressure wave components would have been similarly affected by this calibration error. Last, the present study was conducted in one ethnic group. Our findings may therefore not be translatable to other ethnic groups.

In conclusion, in the present study we show that an age-related deterioration in LV diastolic function begins from an early adult age, well before brachial PP begins to markedly increase. Importantly these changes correlate with enhanced reflected wave pressures starting from an early adult age. In contrast, in the same regression model, neither systemic vascular resistance nor aortic stiffness-related increases in forward wave pressures were associated with tissue Doppler indexes of LV diastolic function independent of reflected wave pressures. The impact of reflected wave pressures on LV diastolic function and the contribution to the relationship between age and LV diastolic function was as strong over the younger as compared to the older adult age. At either a younger or older adult age, the relations of reflected wave pressures with diastolic function were independent of brachial BP. These data raise the question of whether there is a need to target reflected wave function from a very early adult age

to increase LV diastolic functional reserve in midlife, thus preventing LV DD and hence HFpEF in late adult life.

# Chapter 3

## Impact of Stroke Work on the Ability of Left Ventricular Mass to Account for Pressure Effects on Function in a Community with Prevalent Systemic Flow-Dependent Hypertension.

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## 3.1 Abstract

Increases in left ventricular mass (LVM) may not explain LV dysfunction in some populations. We aimed to determine whether the confounding influence of stroke work (SW) on LVM limits the ability of LVM to detect hypertensive LV dysfunction in systemic flow-dependent hypertension. In a community with prevalent systemic flow-dependent hypertension (n=709), arterial haemodynamics, LVM and LV function were determined using central arterial pressure, aortic velocity and diameter measurements in the outflow tract, and echocardiography with tissue Doppler imaging. In multivariate models, SW showed markedly stronger relations with LVM index (LVMI) than blood pressure load (central arterial systolic blood pressure [SBPc], backward wave pressure [Pb], 24-hour SBP) ($p<0.0001$ for comparisons). In contrast, while SBPc, Pb, and 24-hour SBP were inversely associated with myocardial tissue shortening (s') and lengthening (e') velocity, SW was not. With adjustments for SW, positive relationships between SBPc, Pb, or 24-hour SBP and LVMI were eliminated ($p=0.20$ to $p=0.89$), but strong relations between BP and s', e' or E/e' ($p=0.009$ to $p<0.0001$) remained. In mediation analysis, SW fully accounted for BP effects on LVMI, but explained none of the effects of BP on LV function. Hence LVMI accounted for little of the impact of BP load on LV function. Although LVMI beyond SW (inappropriate LVM) improved on relations between LVMI and s', it failed to improve on relations with e' or E/e' and contributed little beyond LVMI to the impact of BP on LV function. In conclusion, in populations with prevalent systemic flow-dependent hypertension, the impact of SW markedly limits the ability of LVM to account for adverse effects of hypertension on LV function.

## 3.2 Introduction

In either primary care settings or in clinical trials of heart failure, hypertension is one of the most frequently cited comorbidities for heart failure (Cleland et al 2002; Krum and, Gilbert 2003). Furthermore, large-scale clinical trials demonstrate an ability of blood pressure (BP) lowering with antihypertensive therapy to prevent the development of heart failure (Dahlof et al 1991, MRC Working Party. Medical Research Council trialists 1992, Kostis et al 1997). More contemporary studies show that achieving BP goals well below usual thresholds has even further benefits for the prevention of heart failure (Wright et al 2015). Thus, identifying hypertensives at risk for the progression to heart failure is essential for clinical practise. In this regard, left ventricular hypertrophy (LVH) is a well-recognised consequence of hypertension that enhances the ability to predict the development of heart failure beyond conventional risk factors and coronary artery disease (Koren et al 1991, Ghali et al 1991, Liao et al 1997). According to the law of La Place, LVH in hypertension is a response to maintain a normal wall stress in the face of an increased BP. However, through renal mechanisms, even primary hypertension may be volume-dependent and in the presence of a volume load, LVH is a necessary response to an increased systemic blood flow and hence cardiac work or stroke work (SW) (the product of BP and stroke volume [SV]). Thus, although LVH in hypertension reflects the adverse effects of a pressure load, the impact of a volume load on systemic flow may confound the ability of LVH to index an accrual of BP effects.

While a pressure load (afterload) has well-recognised detrimental effects to the LV, increases in SW may not have the same effects. Indeed, in risk prediction a need to exclude the non-deleterious impact of SW on LV mass (LVM) was recognised several decades ago (de Simone et al 1998). More recent studies demonstrate a striking ability of LVM beyond the impact of SW to predict events in groups of African ancestry (Anstey et al 2019). In this regard there is now clear evidence for a role of volume-dependent increases in SV, as a dominant pathophysiological change responsible for primary hypertension in groups of African ancestry

living in Africa (Woodiwiss et al 2020, Mmopi et al 2021). In that study (Woodiwiss et al 2020, Mmopi et al 2021) variations in SV and hence peak aortic flow accounted for significantly more uncontrolled primary hypertension than alterations in systemic vascular resistance, the primary haemodynamic change responsible for hypertension in many populations. Whether a volume load with subsequent increases in systemic flow in volume-dependent hypertension contributes to LV dysfunction through pressure effects alone or in-part through a volume load and hence increases in SW is uncertain. Thus, the extent to which the impact of systemic flow-induced increases in SW confounds the ability of LVM to index LV dysfunction, is unknown. Increases in LVM beyond SW (inappropriate LVM or $LVM_{inappr}$) and the regression thereof have been demonstrated to be a strong determinant of systolic function in this population (Woodiwiss et al 2012, Libhaber et al 2013), data consistent with similar relationships noted in other populations (Palmieri et al 1999, Palmieri et al 2001, Celentano et al 2001, De Simone et al 2004, Chinali et al 2006, Chinali et al 2007, Muiesan et al 2007, Cioffi et al 2011). Thus, the impact of LVH on LV function in systemic flow-dependent hypertension may be mediated through a pressure and not a volume load and increases in SW may therefore modify the ability of LVM to detect LV dysfunction. Indeed, a significant component of LVH in this population does not account for the adverse effects of BP on LV function (Bamaiyi et al 2019). However, whether this is explained by the impact of SW on LVH or because LV dysfunction in hypertension is determined by factors that are unrelated to the impact of LVH *per se*, is unknown. In the present study conducted in a population with a high prevalence of volume-dependent hypertension associated with increases in SV (Woodiwiss et al 2020, Mmopi et al 2021), we therefore aimed to determine the extent to which the impact of SW on LVM limits the ability of LVM to detect BP related decreases in tissue Doppler measures of systolic and diastolic LV function.

## 3.3 Methods

### *3.3.1 Study group*

The present study was conducted according to the principles outlined in the Helsinki declaration. The Human Research Ethics Committee (Medical) of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69, M12-04-108 and M17-04-01). Participants gave informed, written consent. The present study design has previously been described (Woodiwiss et al 2009, Norton et al 2012, Booysen et al 2015). In the present sub-study, 709 participants from randomly recruited (from the population census figures of 2001) families of black African descent (Nguni and Sotho chiefdoms) from the South West Township (SOWETO) of Johannesburg, South Africa, with siblings older than 16 years of age had myocardial tissue Doppler imaging (TDI). Of this sample 433 participants had 24-hour ambulatory BP monitoring that met with the European Society of Hypertension guidelines for acceptable measurements (more than 14 and 7 readings for the computation of day and night means, respectively).

### *3.3.2 Clinical and demographic information*

A questionnaire was administered to obtain demographic and clinical data (Woodiwiss et al 2009). Height and weight were measured using standard approaches and participants were considered to be overweight if their body mass index (BMI) was ≥25 kg/m$^2$ and obese if their BMI was ≥30 kg/m$^2$. Laboratory blood tests of renal function, liver function, blood glucose, haematological parameters, and percentage glycated hemoglobin ($HbA_{1c}$) were performed. Diabetes mellitus (DM) was defined as the use of insulin or oral glucose lowering agents or an $HbA_{1c}$ value greater than 6.5%. Serum creatinine concentrations were measured using the Advia Chemistry systems (Siemens) with calibration traceable to isotope dilution mass spectrometry (IDMS). The 4-variable CKD-EPI equation was employed to estimate glomerular filtration rate (eGFR). High quality office brachial blood pressure (BP) measurements were

obtained in the seated position and after 5 minutes of rest, by a trained nurse-technician using a standard mercury sphygmomanometer as previously described (Woodiwiss et al 2009) and according to guidelines. The mean of 5 measurements obtained at least 30 seconds apart was taken as office BP. 24-hour ambulatory BP measurements were performed as previously described (Woodiwiss et al 2009). Hypertension was defined as a mean office BP≥140 mm Hg systolic or ≥90 mm Hg diastolic BP or the use of antihypertensive medication.

*3.3.3 Arterial haemodynamic assessments*

Haemodynamic function was determined from central arterial pressure recordings obtained from pulse wave analysis and aortic velocity and diameter assessments obtained in the outflow tract as described (Woodiwiss et al 2020, Bello et al 2020; Motau et al 2020, Mmopi et al 2021). These measurements were obtained in treated hypertensives while on therapy. However, as indicated in the data analysis, sensitivity analysis was performed in only participants not receiving therapy. After participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry 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). The pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. The peripheral pressure waveform was converted into a central arterial waveform using a validated generalized transfer function incorporated in SphygmoCor software from which central arterial systolic BP (SBPc) was derived. Recordings where the systolic or diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. After central arterial pressure waveforms were acquired, aortic velocity and diameter measurements were obtained by an experienced observer (AJW) with participants in the left lateral decubitus position using an Acuson SC2000 Diagnostic ultrasound system (Siemens Medical Solutions, USA, Inc.). Velocity waveforms were obtained

in the 5-chamber view. Aortic diameter measurements were obtained just proximal to the aortic leaflets in the long axis parasternal view. The largest diameter recorded in the outflow tract in early systole was employed for all analyses. Stroke volume (SV) was determined from the product of velocity-time integral of the aortic velocity wave and aortic root area as described (Woodiwiss et al 2020, Bello et al 2020, Motau et al 2020, Mmopi et al 2021). Stroke work (SW) was determined from the product of SV and peak central arterial SBP generated during ventricular ejection x 0.014 (Woodiwiss et al 2012, Libhaber et al 2013). Proximal aortic characteristic impedance (Zc) was calculated in the time domain as change in pressure/change in flow (Q) from the foot of the pulse wave up until 95% of peak flow (Woodiwiss et al 2020, Bello et al 2020, Motau et al 2020, Mmopi et al 2021). Using Zc values and the flow and pressure waveforms, wave separation analysis was performed and backward wave pressures determined from (aortic PP – QxZc)/2 (Bello et al 2020).

*3.3.4 Echocardiography*

Echocardiographic measurements were performed as previously described (Woodiwiss et al 2009, Norton et al 2012, Booysen et al 2015) by two experienced observers (AJW and CDL) with a low degree of intra- and inter-observer variability, with the participants in the partial left decubitus position. Details of the measurements have previously been described (Woodiwiss et al 2009, Norton et al 2012, Booysen et al 2015). Left ventricular dimensions were determined using two-dimensional directed M-mode echocardiography in the short axis view and these recordings were analysed according to the American Society of Echocardiography convention (Sahn et al 1978). Left ventricular mass was determined using a standard formula (Devereux et al 1986) and indexed (LVMI) to the allometric signal of either body surface area (BSA) or height$^{1.7}$. Left ventricular hypertrophy was identified as an LVMI-ht$^{1.7}$>80 g/m$^{1.7}$ for men and >60 g/m$^{1.7}$ for women. The extent of inappropriate LVM ($LVM_{inappr}$) was determined as previously described (Woodiwiss et al 2012, Libhaber et al 2013) from predicted LVM, where predicted LVM was calculated as 55.37+(6.64 x height$^{2.7}$)+(0.64 x [SBPc x SV x 0.014]) – (18.07

x gender), where male gender=1 and female gender=2, and where SV was derived from outflow tract assessments. Inappropriate LVM was expressed either as actual-predicted LVM in grams, or % actual LVM/predicted LVM. Left ventricular myocardial function was assessed using transmitral velocity and TDI as previously described (Bello et al 2020) and data are shown as the velocity of myocardial shortening (s') and lengthening in early diastole (e') in the lateral and septal walls at the level of the mitral valve and transmitral velocity in early diastole (E)/e', an index of LV filling pressure.

*3.3.5 Data analysis*

For database management and statistical analysis, SAS software, version 9.4 (SAS Institute Inc., Cary, NC) was employed. Continuous variables are expressed as mean (±SD). Dichotomous variables are expressed as percentages. Relationships were evaluated from multivariate linear regression analysis. To determine the contribution of haemodynamic factors or LVMI to relationships, multivariate adjusted product of coefficient mediation analysis, which accounts for hierarchical causal structures, was performed (MacKinnon et al 2007; Baron et al 1986; Krull et al 2001). In regression and mediation analysis adjustments were for age, sex, regular alcohol intake, regular tobacco intake, BMI (or body weight when LVM indexed to allometric signals to height was assessed), DM, treatment for hypertension and heart rate in all analyses and for haemodynamic factors or LVMI where indicated. 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). Relationships were compared using z-statistics. As more women than men volunteered for the present study sensitivity analysis was conducted in sex-specific groups. As antihypertensive therapy may influence the results, sensitivity analysis was also performed in those not receiving therapy.

## 3.4 Results

### *3.4.1 Participant characteristics*

Table 3.1 shows the general characteristics of the study sample. Apart from modest differences in BMI and the proportion who were obese, participants without 24-hour BP measurements that met with pre-specified quality control criteria showed no differences from those with 24-hour BP measurements that met with these criteria (Table 3.2). A high proportion of participants had hypertension and obesity and a high proportion of hypertensives were not receiving antihypertensive therapy. Of the 29.3% receiving antihypertensive therapy, 56.5% were receiving hydrochlorothiazide (HCTZ) as monotherapy, 7.6% a calcium channel blocker in addition to the HCTZ, and 15.8% an angiotensin-converting enzyme inhibitor in addition the HCTZ. 12.0% of treated patients were receiving alternative agents and 8.1% triple therapy. No participants had an ejection fraction (EF) <40% and 4.1% had an EF<50%. Of the sample 39.6% had LVH.

### 3.4.2 Relative impact of pressure versus volume load on LVMI

Although both SW and BP were independently associated with LVMI, the impact of SW on LVMI was markedly greater than that of BP and this was noted in all participants as well as in untreated participants and in women and men (Figure 3.1, Tables 3.3 to 3.6). Importantly, relationships between SW and LVMI were unaffected by adjustments for BP, while relationships between BP and LVMI were abolished by adjustments for SW (Figure 3.1, left panels). In mediation analysis, the impact of BP on LVMI was fully accounted for by an impact of SW, while BP failed to account for any of the impact of SW on LVMI (Figure 3.1, right panels).

### *3.4.3 Relative impact of pressure versus volume load on LV function*

While BP was inversely associated with s' and e' and positively associated with E/e', SV was positively associated with s' and e', but not E/e' and this was noted in all participants as well as in untreated participants and in women and men (Figure 3.2, Tables 3.3 to 3.6).

Table 3.1. Characteristics of participants.

| | |
|---|---|
| n (% male) | 709 (32.4) |
| Age (years) | 47.2±18.1 |
| Body mass index (kg/m$^2$) | 30.0±7.9 |
| % Overweight/obese | 22.9/46.5 |
| % Hypertensive | 49.6 |
| % Treated for hypertension | 29.3 |
| % Uncontrolled hypertension | 35.0 |
| % Diabetes mellitus (DM) | 13.1 |
| % Regular smokers | 16.2 |
| % Regular alcohol intake | 19.5 |
| Estimated GFR (mls/min/1.73m$^2$) | 97.4±22.0 |
| Brachial SBP/DBP (mm Hg) | 128±22/83±13 |
| 24-hour SBP/DBP (mm Hg) | 119±15/73±10 (n=433) |
| SBPc (mm Hg) | 119±22 |
| Pb (mm Hg) | 13±6 |
| Heart rate (beats/min) | 67±12 |
| Stroke volume (SV) (mls/beat) | 78±26 |
| Stroke work (SW) (g/cm$^2$) | 126±40 |
| LVMI-BSA (g/m$^2$) | 68.9±27.6 |
| LVMI-ht$^{1.7}$ (g/m$^{1.7}$) | 62.7±23.1 |
| % with LVH | 39.6 |
| $LVM_{inappr}$ (%) | 113±29 |
| Lateral wall s' (cm/s) | 9.0±2.7 |
| Lateral wall e' (cm/s) | 11.3±4.1 |
| LV E/e' | 7.5±4.2 |

Data shown are mean±SD or proportions. SBP/DBP, systolic and diastolic blood pressure; GFR, glomerular filtration rate; Pb, backward wave pressures; LVMI, left ventricular mass index; BSA, body surface area; $LVM_{inappr}$, LVM beyond that predicted from stroke work or inappropriate LVM expressed as % actual LVM/predicted LVM; s', velocity of myocardial tissue shortening; e', velocity of myocardial tissue lengthening in early diastole; E, transmitral blood flow velocity in early diastole.

Table 3.2. Characteristics of participants with and without 24-hour BP measurements that met with pre-specified criteria.

| | With | Without | p value for comparison |
|---|---|---|---|
| n (% male) | 433 (33.5) | 276 (29.9) | |
| Age (years) | 46.8±18.4 | 47.3±17.1 | |
| Body mass index (kg/m$^2$) | 29.5±7.6 | 30.9±8.3 | p<0.05 |
| % Overweight/obese | 24.5/43.2 | 21.2/51.4 | p<0.05 |
| % Hypertensive | 48.7 | 52.5 | |
| % Treated for hypertension | 28.4 | 30.1 | |
| % Uncontrolled hypertension | 35.3 | 34.9 | |
| % Diabetes mellitus (DM) | 12.7 | 13.4 | |
| % Regular smokers | 15.7 | 16.7 | |
| % Regular alcohol intake | 18.5 | 20.6 | |
| Estimated GFR (mls/min/1.73m$^2$) | 97.9±22.6 | 97.0±20.9 | |
| Brachial SBP/DBP (mm Hg) | 127±22/82±13 | 129±22/83±13 | |
| SBPc (mm Hg) | 118±22 | 120±21 | |
| Pb (mm Hg) | 13±6 | 13±6 | |
| Heart rate (beats/min) | 67±12 | 67±11 | |
| Stroke volume (mls/beat) | 78.8±30.8 | 76.7±34.7 | |
| Stroke work (g/cm$^2$) | 124±38 | 129±37 | |
| LVMI-BSA (g/m$^2$) | 68.7±29.2 | 68.5±23.6 | |
| LVMI-ht$^{1.7}$ (g/m$^{1.7}$) | 62.0±23.1 | 62.7±20.3 | |
| % with LVH | 36.7 | 43.5 | |
| $LVM_{inappr}$ (%) | 113±43 | 114±40 | |
| Lateral wall s' (cm/s) | 9.0±2.6 | 8.9±2.8 | |
| Lateral wall e' (cm/s) | 11.4±4.2 | 11.1±4.0 | |
| LV E/e' | 7.47±4.42 | 7.56±3.75 | |

Data shown are mean±SD or proportions. See Table 3.1 for abbreviations.

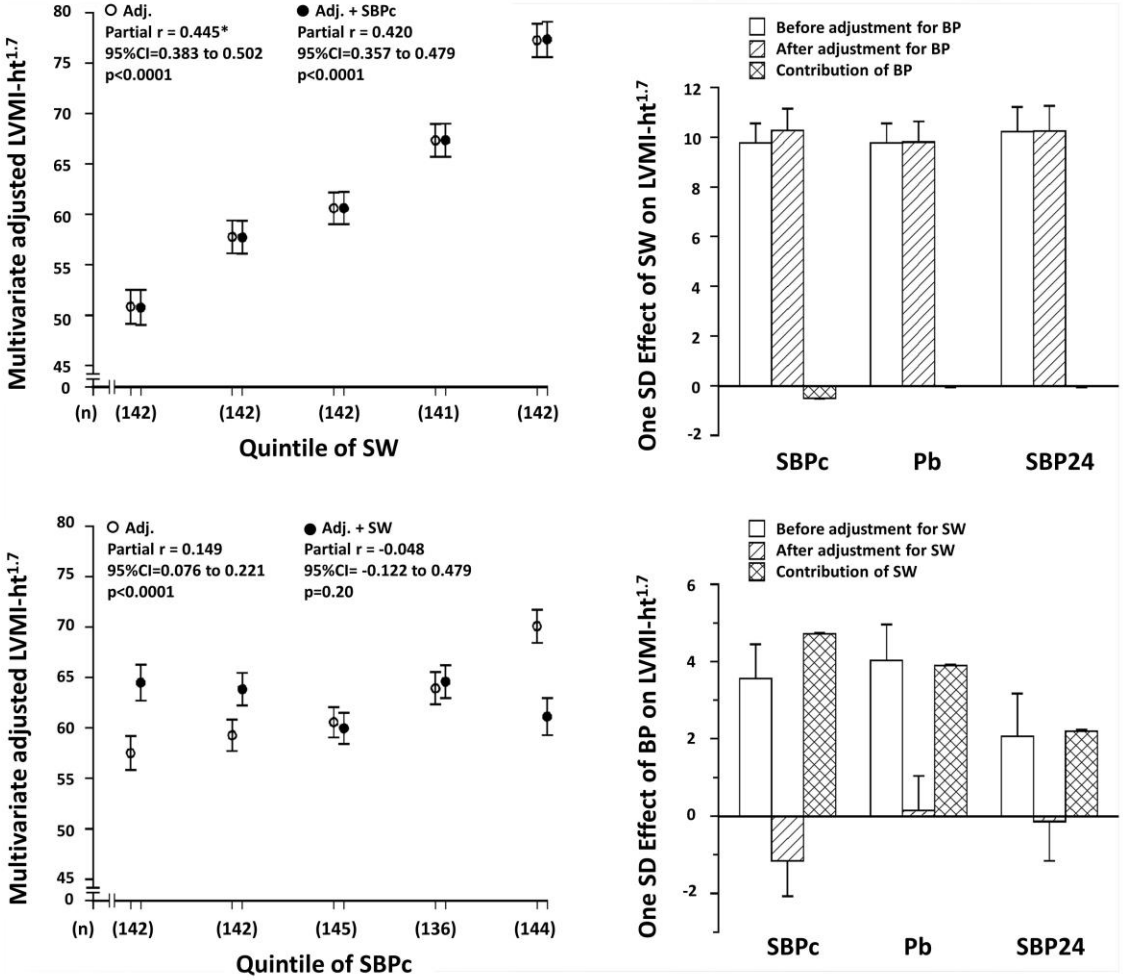


Figure 3.1. Relative contribution of volume (stroke work, SW) versus pressure (BP) load to variations in left ventricular mass index (LVMI-$ht^{1.7}$) in a community sample in Africa (n=709 and 433 with 24-hr BP). Data shown are LVMI across quintiles of SW or central arterial systolic blood pressure (SBPc) before and after adjustments for SBPc and SW respectively (left panels) and the contribution in product of coefficient mediation analysis, of BP or SW to SW or BP effects on LVMI respectively (right panels). Abbreviations are as given in Table 3.1. Adjustments are for SW or BP (as indicated) and age, sex, regular alcohol intake, regular tobacco intake, body weight, DM, treatment for hypertension, and heart rate. *p<0.0001 versus relationship between LVMI and SBPc.

Table 3.3. Relationships (partial r) of haemodynamic factors with left ventricular (LV) mass and function in a community sample in Africa (n=709 and 433 with 24-hr BP).

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | $LVM_{inappr}$ vs |
| Stroke volume | 0.43 (0.37 to 0.48)***† | 0.23 (0.16 to 0.29)*** | -0.57 (-0.63 to -0.52)***† |
| Stroke work | 0.57 (0.51 to 0.61)***† | 0.45 (0.38 to 0.50)***† | -0.57 (-0.62 to -0.51)***† |
| SBPc | 0.15 (0.08 to 0.22)*** | 0.15 (0.08 to 0.22)*** | -0.18 (-0.25 to -0.10)*** |
| Pb | 0.15 (0.08 to 0.23)*** | 0.14 (0.06 to 0.21)** | -0.14 (-0.22 to -0.07)** |
| 24-hour SBP | 0.06 (-0.04 to 0.15) | 0.09 (-0.01 to 0.18) | -0.09 (-0.08 to 0.01) |
| | Lateral wall s' vs | Lateral wall e' vs | E/e' vs |
| Stroke volume | 0.14 (0.06 to 0.22)** | 0.13 (0.05 to 0.21)** | -0.03 (-0.11 to 0.05) |
| Stroke work | 0.02 (-0.05 to 0.10) | -0.05 (-0.12 to 0.03) | 0.14 (0.07 to 0.21)*** |
| SBPc | -0.09 (-0.16 to -0.01)* | -0.18 (-0.25 to -0.10)*** | 0.19 (0.12 to 0.26)*** |
| Pb | -0.08 (-0.16 to -0.01)* | -0.15 (-0.22 to -0.08)*** | 0.20 (0.13 to 0.27)*** |
| 24-hour SBP | -0.11 (-0.20 to -0.01)* | -0.24 (-0.32 to -0.14)*** | 0.20 (0.11 to 0.29)*** |

See Table 3.1. for abbreviations. All relationships are adjusted for age, sex, regular alcohol intake, regular tobacco intake, BMI (except for LVMI-BSA) or body weight (LVMI-$ht^{1.7}$), DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; †p<0.0001 versus SBPc, Pb or 24-hour SBP relationships.

Table 3.4. Relationships (partial r) of haemodynamic factors with left ventricular (LV) mass and function in participants from a community sample in Africa not receiving antihypertensive therapy (n=501 and n=310 with 24-hr BP).

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | $LVM_{inappr}$ vs |
| Stroke volume | 0.47 (0.40 to 0.53)***† | 0.26 (0.18 to 0.33)*** | -0.58 (-0.64 to -0.51)***†† |
| Stroke work | 0.57 (0.51 to 0.63)***†† | 0.41 (0.33 to 0.48)***† | -0.57 (-0.63 to -0.50)***†† |
| SBPc | 0.19 (0.11 to 0.28)*** | 0.21 (0.12 to 0.29)*** | -0.16 (-0.24 to -0.07)** |
| Pb | 0.24 (0.15 to 0.32)*** | 0.20 (0.12 to 0.29)*** | -0.10 (-0.19 to -0.02)* |
| 24-hour SBP | 0.18 (0.06 to 0.28)** | 0.18 (0.07 to 0.29)** | -0.07 (-0.18 to 0.04) |
| | Lateral wall s' vs | Lateral wall e' vs | E/e' vs |
| Stroke volume | 0.20 (0.11 to 0.30)*** | 0.17 (0.07 to 0.26)** | -0.04 (-0.14 to 0.06) |
| Stroke work | 0.07 (-0.02 to 0.16) | -0.03 (-0.12 to 0.06) | 0.13 (0.05 to 0.22)** |
| SBPc | -0.10 (-0.19 to -0.01)* | -0.20 (-0.28 to -0.12)*** | 0.18 (0.10 to 0.27)*** |
| Pb | -0.10 (-0.18 to -0.01)* | -0.15 (-0.24 to -0.07)** | 0.17 (0.08 to 0.25)*** |
| 24-hour SBP | -0.14 (-0.25 to -0.03)* | -0.26 (-0.36 to -0.15)*** | 0.21 (0.10 to 0.32)** |

See Table 3.1 for abbreviations. All relationships are adjusted for age, sex, regular alcohol intake, regular tobacco intake, BMI, DM and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; †p<0.001, ††p<0.0001 versus SBPc, Pb or 24-hour SBP relationships.

Table 3.5. Relationships (partial r) of haemodynamic factors with left ventricular (LV) mass and function in women (n=479 and n=288 with 24-hr BP) from a community sample in Africa.

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | $LVM_{inappr}$ vs |
| Stroke volume | 0.38 (0.31 to 0.45)***† | 0.18 (0.09 to 0.25)*** | -0.63 (-0.69 to -0.57)***†† |
| Stroke work | 0.57 (0.51 to 0.63)***†† | 0.42 (0.34 to 0.49)***†† | -0.63 (-0.68 to -0.57)***†† |
| SBPc | 0.16 (0.07 to 0.25)** | 0.14 (0.05 to 0.23)** | -0.19 (-0.27 to -0.10)*** |
| Pb | 0.14 (0.05 to 0.23)** | 0.12 (0.03 to 0.21)* | -0.18 (-0.26 to -0.09)*** |
| 24-hour SBP | 0.07 (-0.05 to 0.18) | 0.08 (-0.04 to 0.20) | -0.13 (-0.24 to -0.01)* |
| | Lateral wall s' vs | Lateral wall e' vs | E/e' vs |
| Stroke volume | 0.19 (0.10 to 0.29)** | 0.19 (0.09 to 0.28)** | -0.08 (-0.17 to 0.02) |
| Stroke work | -0.01 (-0.10 to 0.08) | -0.07 (-0.15 to 0.03) | 0.15 (0.06 to 0.23)** |
| SBPc | -0.09 (-0.18 to -0.003)* | -0.18 (-0.27 to -0.09)*** | 0.19 (0.10 to 0.27)*** |
| Pb | -0.14 (-0.22 to -0.05)** | -0.14 (-0.23 to -0.06)** | 0.19 (0.10 to 0.28)*** |
| 24-hour SBP | -0.12 (-0.24 to -0.004)* | -0.26 (-0.37 to -0.15)*** | 0.23 (0.11 to 0.34)*** |

See Table 3.1 for abbreviations. All relationships are adjusted for age, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; †p<0.001, ††p<0.0001 versus SBPc, Pb or 24-hour SBP relationships.

Table 3.6**.** Relationships (partial r) of hemodynamic factors with left ventricular (LV) mass index (LVMI), geometric LV remodeling, and LV function in men (n=230 and n=145 with 24-hr BP) from a community sample in Africa.

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | $LVM_{inappr}$ vs |
| Stroke volume | 0.52 (0.42 to 0.60)***† | 0.33 (0.22 to 0.44)*** | -0.41 (-0.53 to -0.28)***† |
| Stroke work | 0.55 (0.45 to 0.63)***†† | 0.48 (0.37 to 0.58)***† | -0.42 (-0.53 to -0.28)***† |
| SBPc | 0.16 (0.03 to 0.29)* | 0.18 (0.05 to 0.31)* | -0.15 (-0.27 to -0.02)* |
| Pb | 0.19 (0.06 to 0.32)** | 0.20 (0.07 to 0.32)** | -0.10 (-0.25 to 0.05) |
| 24-hour SBP | 0.14 (-0.03 to 0.30) | 0.18 (0.01 to 0.33)* | -0.04 (-0.21 to 0.13) |
| | Lateral wall s' vs | Lateral wall e' vs | E/e' vs |
| Stroke volume | 0.08 (-0.07 to 0.23) | -0.05 (-0.20 to 0.10) | -0.04 (-0.19 to 0.11) |
| Stroke work | 0.07 (-0.07 to 0.20) | -0.03 (-0.16 to 0.10) | 0.14 (0.01 to 0.27)* |
| SBPc | -0.09 (-0.22 to 0.04) | -0.16 (-0.29 to -0.03)* | 0.19 (0.06 to 0.32)** |
| Pb | -0.11 (-0.26 to 0.04) | -0.14 (-0.26 to -0.004)* | 0.23 (0.11 to 0.35)** |
| 24-hour SBP | -0.10 (-0.26 to 0.08) | -0.19 (-0.35 to -0.02)* | 0.18 (0.01 to 0.34)* |

See Table 3.1 for abbreviations. All relationships are adjusted for age, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; †p<0.005, ††p<0.0005 versus SBPc, Pb or 24-hour SBP relationships.

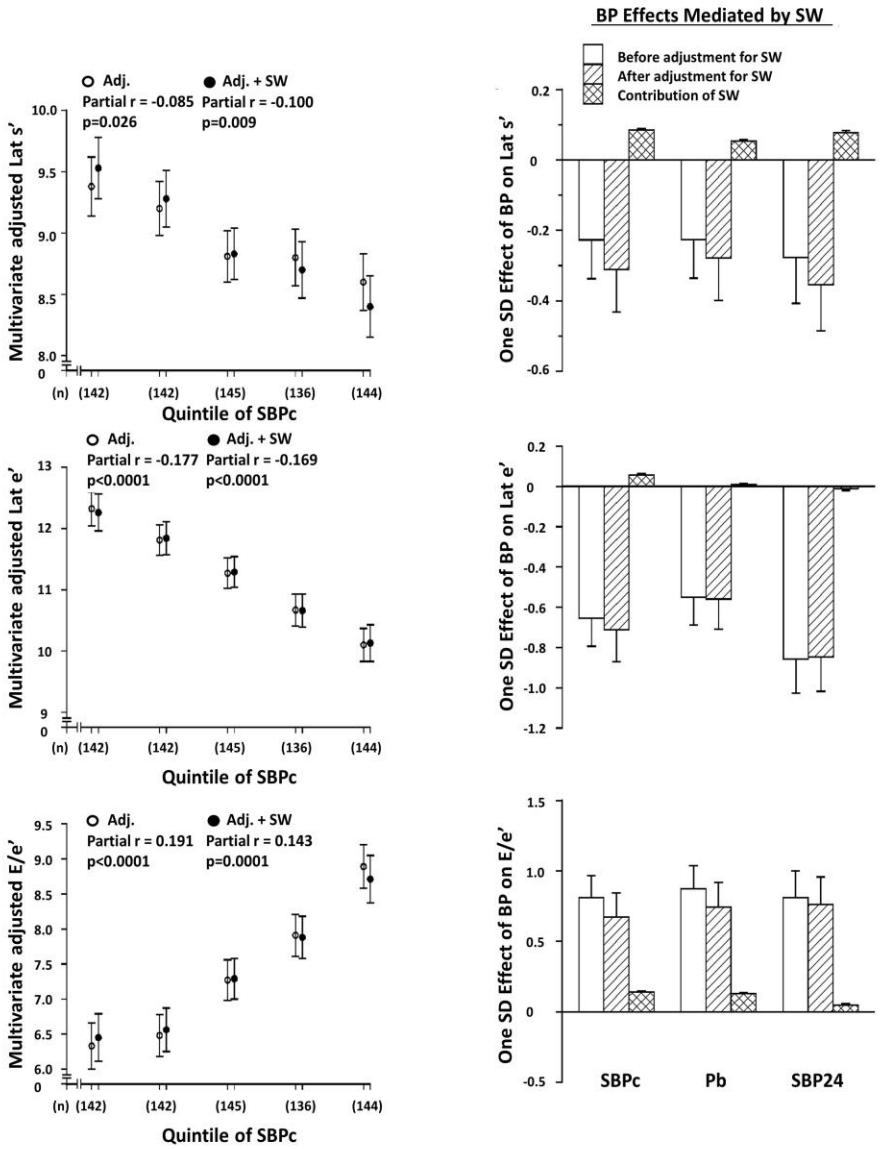


Figure 3.2. Contribution of volume load (stroke work, SW) to relationships between BP and LV function in Africa (n=709). Data shown are relationships (across quintiles of SBPc) between BP and LV function before and after adjustments for SW (left panels) and the contribution, in product of coefficient mediation analysis, of SW to BP effects on LV function (right panels). Abbreviations are as given in Table 3.1. Adjustments are for SW (as indicated) and age, sex, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension and heart rate.

Although, SW was positively associated with E/e', but not s' or e' and this was noted in all participants as well as in untreated participants and in women and men (Tables 3.3 to 3.6), adjustments for SBPc eliminated the relationship between SW and E/e' (p=0.12). Importantly, adjustments for SW failed to modify the relationships between BP and LV function (Figure 3.2, left panels) and in mediation analysis, SW accounted for none of the impact of BP on s' or e' and for only a small proportion (5.9% to 17.2%) of the impact of BP on E/e' (Figure 3.2, right panels).

*3.4.4 Contribution of LVM to relationships between BP and LV function*

As a consequence of the marked contribution of SW to LVMI, but not to LV dysfunction, adjustments for LVMI failed to modify the relationships between BP and LV function (Figure 3.3, left panels) and in mediation analysis accounted for a negligible proportion (3.6% to 7.7%) of the impact of BP on LV function (Figure 3.3, middle panels). Although LVMI was independently associated with LV diastolic, but not systolic function, the contribution was only modestly independent of the impact of BP and this was noted in all participants as well as in untreated participants and in women and men (Tables 3.7 to 3.10). Moreover, the impact of LVMI was less than that of BP in several instances (comparison of standardized β-coefficients in Tables 3.7 tp 3.10). $LVM_{inappr}$ showed significant independent relationships with s', e' and E/e' (Tables 3.7 to 3.10). However, in mediation analysis, $LVM_{inappr}$ accounted for none (in fact added to the impact) of the BP effect on LV dysfunction (Figure 3.3, right panels). This was attributed to the fact that SV was so strongly associated with both SW and BP, that the identification of that portion of LVM not accounted for by SW, also discounted a proportion of LVM determined by BP effects, resulting in SBPc (partial r=-0.18, p<0.0001), and Pb, (partial r=-0.14, p=0.0001) being inversely associated with $LVM_{inappr}$.

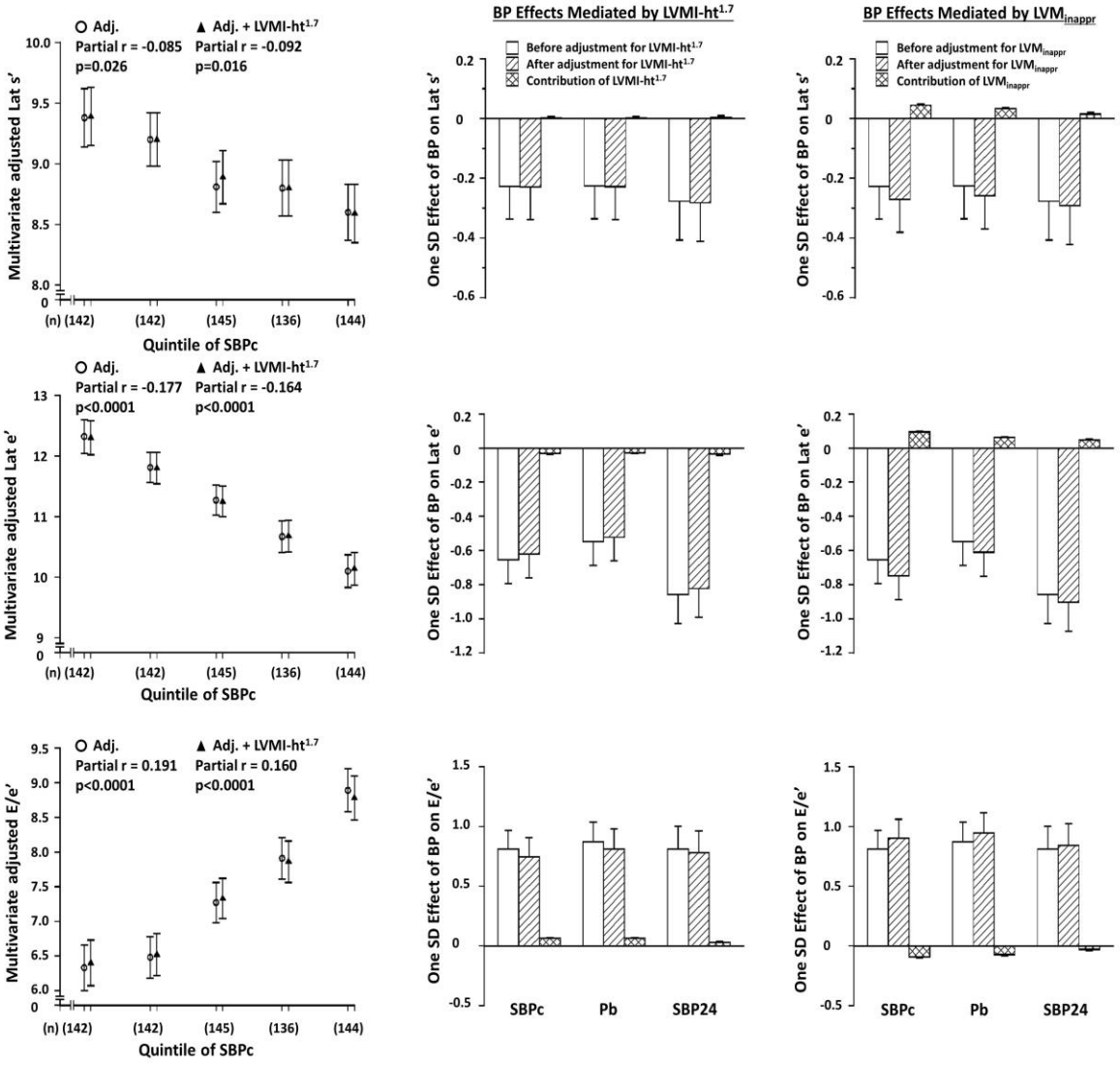


Figure 3.3. Contribution of left ventricular mass to relationships between BP and LV function in Africa (n=709). Data shown are relationships (across quintiles of SBPc) between BP and LV function before and after adjustments for left ventricular mass index (LVMI) (left panels) and the contribution, in product of coefficient mediation analysis, of LVMI (middle panels) or inappropriate LV mass ($LVM_{inappr}$) (right panels) to BP effects on LV function. Abbreviations are as given in Table 3.1. Adjustments are for LVMI (as indicated) and age, sex, regular alcohol intake, regular tobacco intake, body weight (LVMI) or BMI ($LVM_{inappr}$), DM, treatment for hypertension and heart rate.

Table 3.7. Impact (standardized β-coefficient) of left ventricular (LV) mass beyond blood pressure (BP) on variations in LV function in a community sample in Africa (n=709 and 433 with 24-hr BP).

| Models | Lateral wall s' β-coefficient±SEM | Lateral wall e' β-coefficient±SEM | E/e' β-coefficient±SEM |
|---|---|---|---|
| 1. Central arterial SBP | -0.095±0.039* | -0.159±0.035***† | 0.217±0.041***† |
| LVMI-$ht^{1.7}$ | -0.009±0.043 | -0.071±0.033* | 0.091±0.039* |
| 2. Central arterial SBP | -0.110±0.044* | -0.183±0.034***† | 0.230±0.041***† |
| $LVM_{inappr}$ | -0.090±0.040* | -0.108±0.028*** | 0.119±0.037* |
| 3. Pb | -0.105±0.046* | -0.134±0.035*** | 0.232±0.043***† |
| LVMI-$ht^{1.7}$ | -0.009±0.043 | -0.063±0.033 | 0.093±0.039* |
| 4. Pb | -0.106±0.046* | -0.151±0.035***† | 0.243±0.042***† |
| $LVM_{inappr}$ | -0.086±0.040* | -0.098±0.030** | 0.113±0.036** |
| 5. 24-hour SBP | -0.126±0.052* | -0.199±0.040***† | 0.214±0.048***† |
| LVMI-$ht^{1.7}$ | -0.029±0.053 | -0.134±0.042** | 0.066±0.049 |
| 6. 24-hour SBP | -0.118±0.052* | -0.213±0.040***† | 0.215±0.049***† |
| $LVM_{inappr}$ | -0.046±0.048 | -0.100±0.034** | 0.076±0.044 |

See Table 3.1 for abbreviations. Also included in all models are age, sex, regular alcohol intake, regular tobacco intake, BMI ($LVM_{inappr}$) or body weight (LVMI-$ht^{1.7}$), DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of effect; †p<0.05 versus LVMI or $LVM_{inappr}$ effect.

Table 3.8. Impact (standardized β-coefficient) of left ventricular (LV) mass beyond blood pressure (BP) on variations in LV function in participants from a community sample in Africa not receiving antihypertensive therapy (n=501 and n=310 with 24-hr BP).

| Models | Lateral wall s' β-coefficient±SEM | Lateral wall e' β-coefficient±SEM | E/e' β-coefficient±SEM |
|---|---|---|---|
| 1. Central arterial SBP | -0.097±0.050* | -0.203±0.046***† | 0.211±0.050***† |
| LVMI-ht$^{1.7}$ | 0.023±0.052 | -0.037±0.043 | 0.080±0.048 |
| 2. Central arterial SBP | -0.107±0.053* | -0.217±0.044***† | 0.232±0.049*** |
| $LVM_{inappr}$ | -0.109±0.047* | -0.104±0.034** | 0.160±0.044** |
| 3. Pb | -0.106±0.059 | -0.165±0.049**† | 0.174±0.052* |
| LVMI-ht$^{1.7}$ | 0.001±0.055 | -0.031±0.043 | 0.089±0.049 |
| 4. Pb | -0.101±0.054 | -0.160±0.044** | 0.176±0.051** |
| $LVM_{inappr}$ | -0.101±0.047* | -0.106±0.038* | 0.143±0.044** |
| 5. 24-hour SBP | -0.148±0.064*† | -0.226±0.050***† | 0.235±0.062***† |
| LVMI-ht$^{1.7}$ | 0.044±0.071 | -0.082±0.055 | 0.046±0.067 |
| 6. 24-hour SBP | -0.150±0.064* | -0.241±0.049***† | 0.236±0.061*** |
| $LVM_{inappr}$ | -0.073±0.061 | -0.086±0.041* | 0.121±0.054* |

See Table 3.1 for abbreviations. Also included in all models are age, sex, regular alcohol intake, regular tobacco intake, BMI ($LVM_{inappr}$) or body weight (LVMI-ht$^{1.7}$), DM and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of effect; †p<0.05 versus LVMI or $LVM_{inappr}$ effect.

Table 3.9. Impact (standardized β-coefficient) of left ventricular (LV) mass beyond blood pressure (BP) on variations in LV function in women from a community sample in Africa (n=479 and n=288 with 24-hr BP).

| Models | Lateral wall s' β-coefficient±SEM | Lateral wall e' β-coefficient±SEM | E/e' β-coefficient±SEM |
|---|---|---|---|
| 1. Central arterial SBP | -0.110±0.055* | -0.166±0.044*** | 0.225±0.052***† |
| LVMI-ht$^{1.7}$ | -0.020±0.053 | -0.069±0.041 | 0.081±0.049 |
| 2. Central arterial SBP | -0.139±0.056* | -0.199±0.043*** | 0.238±0.052***† |
| $LVM_{inappr}$ | -0.114±0.046* | -0.138±0.034*** | 0.108±0.045* |
| 3. Pb | -0.178±0.055**† | -0.138±0.053** | 0.229±0.052***† |
| LVMI-ht$^{1.7}$ | -0.021±0.052 | -0.066±0.041 | 0.090±0.049 |
| 4. Pb | -0.187±0.055** | -0.166±0.043** | 0.240±0.052***† |
| $LVM_{inappr}$ | -0.123±0.048* | -0.138±0.037** | 0.107±0.045* |
| 5. 24-hour SBP | -0.145±0.060*† | -0.219±0.044*** | 0.253±0.059***† |
| LVMI-ht$^{1.7}$ | -0.030±0.062 | -0.126±0.048** | 0.034±0.059 |
| 6. 24-hour SBP | -0.142±0.062* | -0.230±0.046***† | 0.249±0.061***† |
| $LVM_{inappr}$ | -0.071±0.056 | -0.123±0.039** | 0.060±0.054 |

See Table 3.1 for abbreviations. Also included in all models are age, regular alcohol intake, regular tobacco intake, BMI ($LVM_{inappr}$) or body weight (LVMI-ht$^{1.7}$), DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of effect; †p<0.05 versus LVMI or $LVM_{inappr}$ effect.

Table 3.10. Impact (standardized β-coefficient) of left ventricular (LV) mass beyond blood pressure (BP) on variations in LV function in men from a community sample in Africa (n=230 and n=145 with 24-hr BP).

| Models | Lateral wall s' β-coefficient±SEM | Lateral wall e' β-coefficient±SEM | E/e' β-coefficient±SEM |
|---|---|---|---|
| 1. Central arterial SBP | -0.117 ±0.075 | -0.156±0.063* | 0.216±0.069** |
| LVMI-ht$^{1.7}$ | 0.050±0.074 | -0.036±0.062 | 0.116±0.086 |
| 2. Central arterial SBP | -0.094±0.073 | -0.147±0.059* | 0.221±0.067** |
| $LVM_{inappr}$ | -0.058±0.072 | -0.025±0.052 | 0.164±0.065* |
| 3. Pb | 0.028±0.087 | -0.144±0.065* | 0.259±0.083** |
| LVMI-ht$^{1.7}$ | 0.019±0.076 | -0.034±0.059 | 0.126±0.085 |
| 4. Pb | 0.034±0.083 | -0.134±0.071 | 0.284±0.078*** |
| $LVM_{inappr}$ | 0.064±0.072 | -0.007±0.052 | 0.135±0.064* |
| 5. 24-hour SBP | -0.082±0.102 | -0.182±0.079* | 0.175±0.094 |
| LVMI-ht$^{1.7}$ | -0.088±0.122 | -0.040±0.079 | 0.023±0.093 |
| 6. 24-hour SBP | -0.053±0.097 | -0.175±0.084* | 0.159±0.089 |
| $LVM_{inappr}$ | -0.108±0.092 | -0.044±0.065 | 0.009±0.082 |

See Table 3.1 for abbreviations. Also included in all models are age, regular alcohol intake, regular tobacco intake, BMI ($LVM_{inappr}$) or body weight (LVMI-ht$^{1.7}$), DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of effect; $^{\dagger}$p<0.05 versus LVMI or $LVM_{inappr}$ effect.

## 3.5 Discussion

The main findings of the present study are as follows. In a large community-based study of a group of African ancestry with prevalent volume-dependent hypertension (associated with marked increases in SV) (Mmopi et al 2021, Woodiwiss et al 2021), we explored the extent to which the impact of SW (which is strongly determined by SV) on LVM, limits the ability of LVM to detect the impact of BP on TDI-determined LV dysfunction. In this regard, SW showed markedly stronger relations with LVMI than several determinants of LV pressure afterload including central arterial SBP, backward wave pressures, and 24-hour SBP. Relationships between SW and LVMI were unaffected by adjustments for BP. In contrast, while indexes of LV pressure afterload were associated with TDI measures of LV systolic (s') and diastolic (e' and E/e') dysfunction, SW was only modestly associated with LV E/e'. Consequently, while adjustments for SW abolished relationships between BP and LVMI, adjustments for SW failed to decrease relationships between BP and LV function. Thus, in product of coefficient mediation analysis, SW accounted for BP effects on LVMI, but not function and LVMI failed to account for a significant proportion of the effects of BP on LV function. Although the use of that component of LVM that is accounted for by factors other than SW (inappropriate LVM) improved relations between LVM and s', it failed to improve on relations with e' and E/e'. This was attributed to the strong contribution of SV to BP and resultant inverse relations between BP and inappropriate LVM.

Several studies have highlighted the importance of excluding the contribution of LV workload (the product of SV and SBP) to LVM in order to adequately identify that component of LVH that contributes to LV dysfunction (Palmieri et al 1999, Palmieri et al 2001, Celentano et al 2001, De Simone et al 2004, Chinali et al 2006, Chinali et al 2007, Muiesan et al 2007, Cioffi et al 2011, Woodiwiss et al 2012, Libhaber et al 2013). However, the extent to which increases in SV and hence LV workload confound the ability of LVM to detect LV dysfunction when primary hypertension is strongly determined by SV, has not previously been identified. The recent

description of a major contribution of SV to hypertension in a group of African descent living in South Africa (Mmopi et al 2021, Woodiwiss et al 2020) provided an important opportunity to explore this question. Indeed, in this population, variations in SV and hence peak aortic flow accounted for strikingly more uncontrolled hypertension than that of systemic vascular resistance (Mmopi et al 2021, Woodiwiss et al 2020), the principle haemodynamic change responsible for hypertension in many populations. Indeed, variations in SV and peak aortic Q accounted for hypertension whenever SBP was increased (Mmopi et al 2021). In the present study we show a significantly greater contribution of LV workload (SW) as compared to BP to variations in LVMI in this population and that relationships between SW and LVMI were unaffected by adjustments for BP. Importantly these comparisons of SW or BP relationships with LVMI were between SW and the major components of BP that influence LV structure and function (including SBPc, Pb, and 24-hour SBP). In contrast SW failed to inversely associate with LV s' and e', while BP strongly associated with TDI indexes of LV dysfunction. Thus, while adjustments for SW abolished relations between BP and LVMI, adjustments for SW did not influence relations between BP and TDI measures of LV function (s', e' and E/e'). Furthermore, in product of coefficient mediation analysis, SW accounted for most of the BP effects on LVMI but failed to account for the BP effects on LV function. Consequently, LVMI failed to account for the impact of BP on LV function. These data therefore provide evidence to suggest that when BP is strongly determined by a volume-dependent increase in systemic flow and hence SV, that the dominant effect on LVM is through workload rather than wall stress, while wall stress rather than a volume load has the overriding deleterious effect on LV function. Thus, LVMI has a limited ability to index the adverse effects of BP on LV function in volume-dependent primary hypertension associated with increases in systemic blood flow.

An important statistical approach employed in the present study to complement the multivariate regression analysis, was the use of mediation analysis conducted with appropriate adjustments for potential confounders. In this regard, mediation analysis accounts for

hierarchical causal structures (Baron et al 1986, Krull et al 2001, MacKinnon et al 2007) and our incorporation of this technique is in line with calls for a better appreciation of data structure in epidemiological studies (Normand 2008). In the present study, several hierarchical, or multilevel structures were evaluated. First, we tested the hypothesis that if BP is causally related to LV function, whether an increased LVMI accounts for this effect. Second, we assessed whether if BP is causally related to LVMI, that this effect is accounted for by an increased SW. Third, we evaluated whether if BP is causally related to LV function, that SW accounts for this effect. Although conclusions regarding causal relations cannot be drawn from associations, the findings in mediation analysis caste light on possible hierarchical effects. In this regard, in line with previous findings (Bamaiyi et al 2019) LVMI accounted for very little of the relationship between BP and LV function. In the present study, this was explained by the fact that SW accounted for the relationship between BP and LVMI, but SW accounted for little of the relationship between BP and LV function. These data suggest that if BP is causally related to LV function and LVMI, that the effect on LV function is not through SW, but that the effect on LVMI is mediated by SW. Consequently, LVMI has little role to play as a mediator of BP effects on LV dysfunction.

Several studies have demonstrated that the use of an index of LVH (inappropriate LVM) that excludes the use of SW may enhance the ability to detect LV dysfunction or cardiovascular risk beyond LVMI *per se* (Palmieri et al 1999, Palmieri et al 2001, Celentano et al 2001, De Simone et al 2004, Chinali et al 2006, Chinali et al 2007, Muiesan et al 2007, Cioffi et al 2011, Woodiwiss et al 2012, Libhaber et al 2013, Anstey et al 2019). However, as highlighted by the present study, the efficacy of this approach depends on the ability to account for the impact of SV without excluding BP effects. Indeed, when increases in BP depend on increases in SV as demonstrated in the present population (Woodiwiss et al 2020, Mmopi et al 2021), SW is strongly related to BP. Thus, inappropriate LVM in this circumstance is that component of LVM that excludes not only SW, but also most of the central BP factors (SBPc and Pb) that mainly

explain the adverse effects of hypertension on the LV. Indeed, inappropriate LVM in the population studied by us was inversely associated with the central arterial BP factors that mainly account for LV dysfunction.

Although we have previously demonstrated using regression and mediation analyses that the relationship between in-office brachial BP on LV diastolic dysfunction is not explained to any significant extent by LVMI (Bamaiyi et al 2019), in that study we had not provided an explanation for these findings. Moreover, we failed to evaluate the extent to which LVMI could account for the major BP changes responsible for decreases in LV function (24-hour SBP for s' and Pb or SBPc for e' and E/e'). In this regard, in the present study we show that the major explanation for the limited ability of LVMI to account for BP effects on LV dysfunction is that in volume-dependent hypertension with striking increases in systemic blood flow, SW accounts for far more of the variability of LVM than wall stress produced by increases in BP. In contrast, SV and hence SW has relatively little adverse effect on several aspects of LV function, while BP has consistent deleterious effects on LV function. This is in-part in-keeping with our previous proposal that LV dysfunction is mediated by changes in the LV beyond LVH (Bamaiyi et al 2019). Importantly however, in contrast to what was originally suggested (Bamaiyi et al 2019), this effect is not through a differential impact of BP on LVM and function, but rather through non-BP related effects (SW) on LVH. With respect to the lack of ability of LVH to account for in-office brachial BP effects on LV function previously described (Bamaiyi et al 2019), this could be accounted for in-part by differential BP effects on LV structure versus function. In this regard, as compared to office BP measurements performed at the brachial artery, out-of-office or central arterial BP may be more important for detecting LV dysfunction as opposed to LVMI or *vice versa*. However, in the present study, we evaluated all possible BP effects and noted that LVMI failed to account for a significant component of any BP effect on LV function.

In the present community, the prevalence of overweight and obesity was striking. As obesity is well recognised as producing a volume overload and hence an increased systemic

flow, this may suggest that the confounding influence of volume overload and increases in systemic flow and hence SW on the ability of LVMI to account for LV functional changes, depends on body size. However, as previously described (Woodiwiss et al 2020), the marked age-related increases in SV that account for uncontrolled hypertension in the present population occurs irrespective of whether SV is indexed for BSA or not. Indeed, groups of African ancestry are often cited as developing hypertension that is strongly related to renal fluid retention (Woodiwiss et al 2020). Moreover, an even stronger relationship between SV and LVMI was noted in the present study when LVM was indexed for BSA (which in-part accounts for obesity effects), rather than height$^{1.7}$, which acknowledges a possible role of obesity-induced LVH as a cause of LV dysfunction. Furthermore, in all analyses, relationships were adjusted for body weight (with LVMI-ht$^{1.7}$) or body mass index (LVMI-BSA). Thus, the confounding influence of volume overload with consequent increases in SV and hence SW on the ability of LVMI to account for LV functional changes as noted in the present community, is independent of body size.

The clinical implications of the present study, although speculative, are worthy of consideration. In this regard, caution should be exercised in the interpretation of the findings. The present study does not suggest that LVMI will not predict the development of heart failure in systemic flow-dependent hypertension. Indeed, we show relationships between LVMI and LV diastolic functional abnormalities beyond in-office brachial BP (Bamaiyi et al 2019). These relationships would nonetheless be explained mainly by the ability of LVMI to index uncontrolled increases in SV and hence SW rather than BP. However, in the present study SW did independently associate with E/e', possibly because a volume overload may contribute to increases in filling pressure. Thus, even if LVMI is largely explained by an impact of SW, LVMI may be useful in risk prediction for heart failure with a preserved ejection fraction. However, this approach may be limited in the prediction of risk related to all forms of hypertensive heart failure (heart failure associated with a reduced LV systolic function). Furthermore, LVMI will not provide

an accurate index of the accrual of all of the adverse effects of BP on diastolic LV function. Thus, if echocardiography is being employed for risk prediction, in volume-dependent hypertension where increases in systemic blood flow are an important cause of increases in BP, measures of systolic and diastolic LV function (TDI assessments) may be preferred for risk prediction. Nevertheless, in resource-limited or primary care settings without access to echocardiography, electrocardiographic LVH may still offer an additional index to enhance the prediction of the risk for heart failure or alternative events caused by increases in BP in flow-dependent hypertension. Longitudinal studies are therefore required in volume-dependent forms of hypertension to determine whether LVM or function best predict the development of heart failure. Moreover, further studies are required to determine the ability of electrocardiographic LVH to detect LV dysfunction or the ability of either echocardiographic or electrocardiographic LVH to associate with cardiovascular events caused by flow-dependent hypertension.

There are several limitations of the present study. As the present study was cross-sectional in design, no conclusions regarding cause and effect can be drawn. Second, we determined SV from measurements in the outflow tract (product of velocity-time integral and aortic root cross-sectional area) rather than with more advanced approaches such as 3-dimensional cardiac magnetic resonance imaging (MRI). However, the approach employed in the present study is not limited by echocardiographic approaches that assume a uniform 3-dimensional LV geometry. In the present study we also show strong relations between outflow tract-derived SV and LVMI, an effect that if limited by the use of less accurate techniques than MRI, would have biased against, rather than in favour of our findings. Furthermore, the age-related increases in SV previously reported on (Woodiwiss et al 2020) were markedly consistent and showed a high degree of reproducibility when comparing outflow tract and biplane Simpson methods, assessments which employ very different measures to calculate SV. Moreover, while SV explains the low renin state in this population (Woodiwiss et al 2020), a characteristic feature of hypertension in those of African ancestry, vascular determinants of BP failed to so

(Woodiwiss et al 2020). In addition, while in more recent analysis (Malan et al, in-press) variations in SV were strongly associated with renal function, including tubular reabsorption of $Na^+$, vascular determinants of BP were not. A third possible limitation is that we determined SV at a single moment of time in the day and hence we were unable to account for possible diurnal variations. In this regard, impedance cardiography has been employed to determine SV continuously, rather than at single points in time (Mansouri et al 2018), and hence offers the opportunity to determine diurnal changes using non-invasive techniques. However, SV determined using impedance cardiography shows limited agreement as compared to SV obtained using MRI (Trinkmann et al 2016, Borzage et al 2017). Fourth, a significant proportion of treated hypertensives were receiving diuretic therapy at the time of measurement, which may have decreased blood volume and systemic flow, thus limiting the relationships noted. However, again this would have biased against our findings. This is nevertheless unlikely as the relationships noted between SV and LVMI were similarly striking in sensitivity analysis performed in untreated participants, a significant proportion of whom were hypertensives at the time. Last, in the present study, calibration of the radial waveform from brachial BP measurements ignores amplification of BP from brachial to radial arteries (Picone et al 2015). Hence, aortic pressures may have been underestimated using the current approach.

In conclusion, in the present study conducted in a community where uncontrolled primary hypertension is strongly driven by systemic flow (Woodiwiss et al 2020, Mmopi et al 2021) we show that while variations in LVMI are largely accounted for by increases in SW rather than BP load, variations in TDI determined LV systolic and diastolic function are largely explained by BP load (central arterial SBP, backward wave pressures and 24-hour SBP). Thus, in product of coefficient mediation analysis, BP effects on LVMI, but not LV function were largely mediated by SW and consequently LVMI accounted for little of the impact of BP on LV function. These data suggest that through a confounding effect of increases in SW on LVMI, that LVMI has a limited ability to detect the adverse effects of BP on LV function in populations with

prevalent systemic flow-dependent primary hypertension. In the assessment of the risk for heart failure, measures of LV function (TDI assessments of systolic and diastolic function) may therefore be preferred to LVMI in some forms of hypertension.

# Chapter 4

## Hemodynamic and Functional Correlates of Concentric versus Eccentric Left Ventricular Hypertrophy in a Community-Based Sample with Prevalent Volume-Dependent Hypertension.

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## 4.1 Abstract

Whether in populations with prevalent volume-dependent primary hypertension, concentric left ventricular (LV) remodelling beyond hypertrophy (LVH) represents the impact of a pressure rather than a volume overload is unclear. Using central arterial pressure, and aortic velocity and diameter measurements in the outflow tract and echocardiography, we determined the factors that associate with concentric LVH or remodelling in the LV short axis in a community of African ancestry (n=709) with prevalent volume-dependent primary hypertension. Both left ventricular mass index (LVMI) and RWT were positively and independently associated with end diastolic volume (EDV), stroke volume (SV) and peak aortic flow (Q) ($p<0.05$ to $<0.0001$). However, neither LVMI nor RWT were positively and independently associated with systemic vascular resistance (SVR), or aortic characteristic impedance (Zc) or inversely associated with total arterial compliance (TAC). Consequently, both concentric ($p<0.0001$) and eccentric ($p<0.0001$) LVH were associated with similar increases in EDV, SV, and either office brachial, central arterial or 24-hour blood pressures, but neither increases in SVR or Zc nor decreases in TAC. Left ventricular RWT, but not LVMI was nevertheless independently and inversely associated with myocardial systolic function (midwall fractional shortening and LV wall myocardial shortening velocity [s']) ($p<0.05$ to $<0.005$) and decreases in LV systolic function were noted in concentric ($p<0.05$), but not eccentric LVH. In conclusion, in volume-dependent primary hypertension, concentric LVH is determined as much by volume-dependent increases in systemic flow and an enhanced BP as eccentric LVH. Concentric remodelling nevertheless reflects decreases in systolic function beyond LVH.

## 4.2 Introduction

Left ventricular hypertrophy (LVH) is a well-recognised consequence of hypertension that enhances risk prediction beyond conventional risk factors and coronary artery disease (Koren et al 1991, Ghali et al 1992, Liao et al 1997). Structural remodelling of the LV in hypertension nonetheless includes not only hypertrophy, but also geometric changes defined by mass or wall thickness relative to internal volumes or diameters. In this regard, as compared to a normal LV geometry, concentric LV remodeling, as indexed by either an increased wall thickness-to-internal radius in the LV short axis (relative wall thickness-RWT) or an increased LV mass (LVM)-to-volume ratio, predicts cardiovascular risk beyond that noted in those with a more eccentric LV geometry (Koren et al 1991, Verdecchia et al 1995, Krumholz et al 1995, Pierdomenico et al 2004, Muiesan et al 2004, Milani et al 2006, Bluemke et al 2008, Bang et al 2014, Tsao et al 2015, Cuspidi et al 2015). Left ventricular remodeling is generally viewed as a compensatory response to increased LV loading conditions, and hence to reflect the impact of cumulative changes in LV loads over time. In this regard, conventional thought is that a more concentric LV (remodelling or hypertrophy) indexes a worse pressure load on the heart, while a more eccentric LV indexes more of a volume load. However, the implications of a concentric LV beyond LVH in populations generally considered to have prevalent volume-dependent hypertension are uncertain.

According to the Law of La Place, the LV concentrically remodels as an adaptation that maintains a normal wall stress in the face of a pressure load, and as such a greater RWT may indirectly reflect less well controlled blood pressures (BP). In contrast, in the presence of a volume load, as long as overt dilatation of the LV has not occurred, eccentric LVH may primarily reflect a consequent increase in stroke volume (SV) produced by Frank-Starling effects on the LV. Thus, as long as the increased SV has not translated into poor BP control, eccentric LVH may not always predict a worse outcome than those without LVH (Bang et al 2014, Cuspidi et al 2015). The remodelling process is therefore thought to provide information as to the

pathophysiological mechanism that requires targeting with the presence of concentric LVH suggesting worse BP control. Nevertheless, a high prevalence of concentric LVH as identified from RWT assessments in the short axis of the LV (Bamaiyi et al 2019; Norton et al 2019) has been reported in a community recently demonstrated to show prevalent volume-dependent, low renin hypertension strongly associated with an age-related increase in LV filling volumes and hence SV (Woodiwiss et al 2020, Mmopi et al 2021). Importantly, a strong age-related increase in LV mass index (LVMI), a change well recognised as contributing to concentric remodelling, was also noted (Bello et al 2020). These data therefore raise the question as to whether a more concentric LV, as identified from short axis dimensions, indeed reflects less of a volume and more of a pressure overload state in those with volume-dependent forms of hypertension? In this regard, in order to preserve systolic chamber function concentric LVH may also occur as a response to decreases in intrinsic myocardial systolic function, a change frequently noted in populations with prevalent volume-dependent hypertension (Woodiwiss et al 2012, Libhaber et al 2013). Moreover, concentric LV remodelling may accompany LV diastolic dysfunction, changes also frequently noted in populations with prevalent volume-dependent hypertension (Bamaiyi et al 2019, Bello et al 2020). In this regard, the cellular mechanisms responsible for diastolic dysfunction in hypertension may also cause a concentric LV (Badenhorst et al 2003). In the present study we therefore aimed to identify the hemodynamic and LV functional correlates of concentric LV remodelling beyond hypertrophy in a community with a high prevalence of volume-dependent, low renin hypertension (Woodiwiss et al 2020, Mmopi et al 2021).

## 4.3 Methods

### *4.3.1 Study group*

The present study was conducted according to the principles outlined in the Helsinki declaration. The Human Research Ethics Committee (Medical) of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-

69, M12-04-108 and M17-04-01). Participants gave informed, written consent. The present study design has previously been described (Woodiwiss et al 2009, Norton et al 2012, Woodiwiss et al 2012, Libhaber et al 2013, Booysen et al 2015, Bamaiyi et al 2019, Norton et al 2019, Woodiwiss et al 2020, Bello et al 2020, Mmopi et al 2021). In the present sub-study 824 participants from randomly recruited (from the population census figures of 2001) families of black African descent (Nguni and Sotho chiefdoms) from the South West Township (SOWETO) of Johannesburg, South Africa, with siblings older than 16 years of age with high-quality velocity assessments in the outflow tract (a smooth velocity waveform with a dense leading [outer] edge and a clear maximum velocity) were evaluated. In this regard, nuclear families identified from census figures living in SOWETO of black African ancestry were assigned a number. Selection of families was based on the use of random number generator software. Of the 800 nuclear families approached, 451 (56.4%) agreed to participate in the study. There were no other inclusion/exclusion criteria. Of these participants all had standard echocardiographic assessments and 709 had myocardial tissue Doppler imaging (TDI). Of this sample 433 participants had 24-hour ambulatory BP monitoring that met with the European Society of Hypertension guidelines for acceptable measurements (more than 14 and 7 readings for the computation of day and night means, respectively). Of the 709 who had TDI, 518 had assessments of renin-angiotensin-aldosterone system concentrations.

*4.3.2 Clinical and demographic information*

A questionnaire was administered to obtain demographic and clinical data (Woodiwiss et al 2009). Height and weight were measured using standard approaches and participants were considered to be overweight if their body mass index (BMI) was ≥25 kg/m$^2$ and obese if their BMI was ≥30 kg/m$^2$. Laboratory blood tests of renal function, liver function, blood glucose, hematological parameters, and percentage glycated hemoglobin ($HbA_{1c}$) were performed. Diabetes mellitus (DM) was defined as the use of insulin or oral glucose lowering agents or an

$HbA_{1c}$ value greater than 6.5%. Serum creatinine concentrations were measured using the Advia Chemistry systems (Siemens) with calibration traceable to isotope dilution mass spectrometry (IDMS). The 4-variable CKD-EPI equation was employed to estimate GFR. High quality office brachial blood pressure (BP) measurements were obtained in the seated position and after 5 minutes of rest, by a trained nurse-technician using a standard mercury sphygmomanometer as previously described (Woodiwiss et al 2009) and according to guidelines. The mean of 5 measurements obtained at least 30 seconds apart was taken as office BP. 24-hour ambulatory BP measurements were performed as previously described (Woodiwiss et al 2009). Hypertension was defined as a mean office BP≥140 mm Hg systolic or ≥90 mm Hg diastolic BP or the use of antihypertensive medication. Circulating renin and aldosterone concentrations were determined as previously described (Woodiwiss et al 2020). Plasma renin concentrations were measured using an immunoradiometric technique (Renin III Generation, Cisbio International, Ceze, France) and serum aldosterone concentrations using an $^{125}I$ radioimmunoassay (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA).

*4.3.3 Arterial hemodynamic assessments*

Arterial function was determined from central arterial pressure recordings obtained from pulse wave analysis and aortic velocity and diameter assessments obtained in the outflow tract as described (Woodiwiss et al 2020, Mmopi et al 2021, Bello et al 2020) After participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry 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). The pulse wave was calibrated by manual measurement (auscultation) of brachial BP taken immediately before the recordings. The peripheral pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphygmoCor software. Recordings where the systolic or diastolic variability of

consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV were discarded. After central arterial pressure waveforms were obtained aortic velocity and diameter measurements were obtained by an experienced observer (AJW) with participants in the left lateral decubitus position using an Acuson SC2000 Diagnostic ultrasound system (Siemens Medical Solutions, USA, Inc.). Velocity waveforms were obtained in the 5-chamber view. Aortic diameter measurements were obtained just proximal to the aortic leaflets in the long axis parasternal view. The largest diameter recorded in the outflow tract in early systole was employed for all analyses.

Stroke volume was determined from the velocity-time integral of the aortic velocity wave and aortic root diameter using standard approaches. Systemic vascular resistance (SVR) was calculated from mean arterial pressure (MAP) and cardiac output (MAP=SVR x CO), assuming right atrial pressure = 0 mm Hg. Cardiac output was determined from SV x heart rate. To identify the hemodynamic determinants of pulsatile load. aortic flow waveforms were first generated from aortic velocity and diameter measurements as described (Woodiwiss et al 2020, Bello et al 2020, Mmopi et al 2021). Characteristic impedance (Zc) was calculated in the time domain as change in pressure/change in flow from the foot of the pulse wave up until 95% of peak flow (Woodiwiss et al 2020, Bello et al 2020, Mmopi et al 2021). Using Zc values and the flow and pressure waveforms, wave separation analysis was performed to obtain backward wave pressures based on the following formulae: Backward wave pressure=(aortic PP – QxZc)/2), where Q=flow (Bello et al 2020). Total arterial compliance (TAC) was calculated as SV/aortic pulse pressure (Woodiwiss et al 2020, Mmopi et al 2021).

*4.3.4 Echocardiography*

Echocardiographic measurements were performed as previously described (Woodiwiss et al 2009, Woodiwiss et al 2012, Norton et al 2012, Libhaber et al 2013, Booysen et al 2015, Bamaiyi et al 2019, Norton et al 2019, Bello et al 2020) by two experienced observers (AJW and CDL) with a low degree of intra- and inter-observer variability, with the participants in the partial

left decubitus position. Details of the measurements have previously been described (Woodiwiss et al 2009, Woodiwiss et al 2012, Norton et al 2012, Libhaber et al 2013, Booysen et al 2015, Bamaiyi et al 2019, Norton et al 2019, Bello et al 2020). Left ventricular dimensions were determined using two-dimensional directed M-mode echocardiography in the short axis view and these recordings were analysed according to the American Society of Echocardiography convention (Sahn et al 1978). Left ventricular mass was determined using a standard formula (Devereux et al 19867) and indexed (LVMI) to the allometric signal of height$^{1.7}$(Chirinos et al 2010). Left ventricular end systolic (ESV) and diastolic (EDV) volumes and chamber systolic function as determined from ejection fraction (EF), were also assessed, but from the biplane Simpson approach. Left ventricular myocardial and chamber systolic function in the short axis of the LV was determined from endocardial (FSend) and midwall (FSmid) fractional shortening also using dimensions obtained in the short axis of the LV as previously described (Woodiwiss et al 2012, Libhaber et al 2013). Left ventricular myocardial systolic function was further determined using tissue Doppler indices (TDI)(lateral and septal wall velocity of myocardial shortening [s']). Left ventricular diastolic function was assessed using transmitral velocity and tissue Doppler imaging as previously described (Bamaiyi et al 2019, Norton et al 2019, Bello et al 2020) and data are shown as the velocity of myocardial lengthening in early diastole (e') in the lateral and septal walls and transmitral velocity in early diastole (E)/e', an index of LV filling pressure. Left ventricular RWT was determined from end diastolic internal diameters and wall thickness values in the short axis of the LV. Wall thickness was determined from the mean of the septal and posterior walls. Left ventricular hypertrophy was identified as an LVMI-ht$^{1.7}$>80 g/m$^{1.7}$ for men and >60 g/m$^{1.7}$ for women (Chirinos et al 2010). Concentric short axis LV remodelling and concentric LVH were defined as a RWT≥0.42 or ≥0.44 (upper 90 or 95% confidence interval of RWT in 306 normotensive, non-obese, non-diabetic participants).

*4.3.5 Data analysis*

For database management and statistical analysis, SAS software, version 9.4 (SAS Institute Inc., Cary, NC) was employed. Continuous variables are expressed as mean (±SD). Dichotomous variables are expressed as percentages. Relationships were evaluated from multivariate linear (continuous analysis) or logistic (discrete analysis) regression analysis. In regression analysis adjustments were for age, sex, regular alcohol intake, regular tobacco intake, BMI (or body weight for LVMI-$ht^{1.7}$), DM, treatment for hypertension and heart rate in all analyses and for hemodynamic factors or LVMI where indicated. 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). Relationships were compared using z-statistics. As more women than men volunteered for the present study sensitivity analysis was conducted in sex-specific groups. As antihypertensive therapy may influence the results, sensitivity analysis was also performed in those not receiving therapy. Moreover, as the impact of haemodynamic factors or LVMI may be greater in hypertensives as opposed to normotensives, sensitivity analysis was conducted in hypertensives and normotensives separately.

## 4.4 Results

*4.4.1 Participant characteristics according to categories of LV remodelling*

Apart from modest differences in the BMI and the proportion who were obese, 0participants without 24-hour BP measurements that met with prespecified quality control criteria showed no differences from those with 24-hour BP measurements that met with these criteria (data not shown). Similarly, apart from modest differences in the proportion of women without renin and aldosterone measurements as compared to those with these measurements (70.5% vs 62.9%, $p<0.05$) and consequently a modestly lower LVMI-$ht^{1.7}$ ($p<0.05$), no differences were noted between these participants (data not shown). No participants had an

EF<40% and 4.1% had an EF<50%. Of the sample 39.6% had LVH, 8.6% had concentric remodelling, 9.4% concentric LVH and 30.2% eccentric LVH (Table 4.1). Based on end diastolic diameter assessments (EDD>5.5 cm) no participants had concentric, dilated LVH. However, a significant proportion had eccentric, dilated LVH (5.8%). As compared to those with a normal LV geometry and LVMI, those with concentric remodelling but without LVH were older and had a higher SBP (Table 4.1). However, as compared to those with a normal LV geometry and LVMI, those with either concentric or eccentric LVH were older and markedly more obese and hypertensive (Table 4.1). No differences in risk factors were noted between those with concentric versus eccentric LVH (Table 4.1).

*4.4.2 Hemodynamic correlates of LV remodelling*

In keeping with the presence of prevalent volume-dependent hypertension, volume and hence systemic blood flow-related hemodynamic correlates (EDV, SV and peak aortic Q) were strongly positively and independently associated with LVMI and to a lesser extent with RWT as well (Tables 4.2 to 4.7). These relationships with LVMI were noted in several subgroups including untreated participants (Table 4.3), women and men (Tables 4.4 and 4.5) and hypertensives and normotensives (Tables 4.6 and 4.7). Relationships between systemic flow and RWT were also noted in several subgroups (Table 4.2 to 4.7), but not in women (Table 4.4). Although beyond confounders, eGFR was also independently associated with LVMI (LVMI-$ht^{1.7}$: partial r=-0.12, CI=-0.20 to -0.03, p<0.005) and RWT (partial r=-0.19, CI=-0.27 to -0.11, p<0.0001), adjustments for eGFR did not alter relationships between SV and LVMI (LVMI-$ht^{1.7}$: partial r=0.28, CI=0.21 to 0.36, p<0.0001) or RWT (partial r=0.13, CI=0.04 to 0.21, p<0.005) (see Table 4.2 for relationships before adjustments for eGFR). In contrast to the strong independent relations between systemic flow-related haemodynamic correlates and LVMI or RWT, of the vascular factors, neither SVR, nor Zc showed direct relations with LVMI or remodelling and TAC failed to show inverse relations with LVMI or remodelling (Tables 4.2 to 4.7).

Table 4.1. Characteristics across categories of left ventricular (LV) remodelling.

| LV mass index (LVMI)→<br>LV geometry→ | Normal<br>Eccentric | Normal<br>Concentric | Increased (LVH)<br>Concentric | Increased (LVH)<br>Eccentric |
|---|---|---|---|---|
| n (% male) | 367 (46.1) | 61 (36.1) | 67 (16.4**) | 214 (12.4**) |
| Age (years) | 40.8±15.8 | 51.9±16.8** | 57.9±19.3** | 53.1±17.4** |
| Body mass index (kg/m$^2$) | 26.8±6.6 | 28.2±7.0 | 35.7±8.0** | 34.4±7.3** |
| % Overweight/obese | 27.1/28.5 | 24.6/37.7 | 13.4/76.1** | 18.4/70.9** |
| % Hypertensive | 37.7 | 59.0 | 74.6** | 62.7** |
| % Treated for hypertension | 17.6 | 39.3 | 56.7** | 46.1** |
| % Diabetes mellitus (DM) | 8.7 | 16.4 | 19.4** | 17.5** |
| % Regular smokers | 21.4 | 24.6 | 10.4* | 6.4** |
| % Regular alcohol intake | 24.9 | 21.3 | 7.5** | 13.4** |
| Brachial SBP/DBP (mm Hg) | 123±20/81±12 | 130±21*/83±13 | 135±24**/85±14** | 134±22**/84±13** |
| 24-hour SBP (mm Hg) | 116±15 (n=230) | 123±15** (n=44) | 122±15* (n=41) | 123±15** (n=118) |
| 24-hour DBP (mm Hg) | 72±10 (n=230) | 76±10* (n=44) | 74±10 (n=41) | 75±10** (n=118) |
| Central arterial SBPc (mm Hg) | 113±20 | 121±20 | 127±20** | 125±20** |
| Backward wave pressures (Pb)(mm H | 12±6 | 14±7** | 5±6** | 15±6** |
| LVMI (g/m$^2$) | 56.6±22.2 | 61.9±23.6 | 92.4±27.0** | 84.5±24.4** |
| LVMI (g/m$^{1.7}$) | 49.7±15.7 | 50.3±16.6 | 84.4±19.0** | 81.8±17.2** |
| LV relative wall thickness (RWT) | 0.33±0.05 | 0.48±0.05** | 0.49±0.06** | 0.35±0.05 |

Data shown are mean±SD or proportions. SBP, brachial systolic blood pressure; DBP, brachial diastolic blood pressure; LVH, left ventricular hypertrophy. *p<0.05, **p<0.005 versus normal LVMI and geometry.

Table 4.2. Relationships (partial r) of hemodynamic factors with left ventricular (LV) mass index (LVMI) and geometric LV remodelling in a community sample in Africa (n=709 and 433 with 24-hr BP).

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-ht$^{1.7}$ vs | RWT vs |
| Stroke volume | 0.43 (0.37 to 0.48)***†† | 0.23 (0.16 to 0.29)***† | 0.12 (0.05 to 0.19)*** |
| Peak aortic Q | 0.16 (0.09 to 0.22)*** | 0.11 (0.04 to 0.17)** | 0.10 (0.03 to 0.17)** |
| EDV | 0.43 (0.37 to 0.48)***†† | 0.25 (0.18 to 0.31)**†† | 0.08 (0.01 to 0.15)* |
| SVR | -0.40 (-0.46 to -0.34)***†† | -0.20 (-0.26 to -0.13)***†† | 0.03 (-0.04 to 0.10) |
| Zc | -0.01 (-0.08 to 0.206) | 0.05 (-0.02 to 0.11) | -0.02 (-0.09 to 0.05) |
| TAC | 0.26 (0.19 to 0.32)***†† | 0.09 (0.02 to 0.16)* | 0.001 (-0.07 to 0.07) |
| SBPc | 0.15 (0.08 to 0.22)*** | 0.15 (0.08 to 0.22)*** | 0.10 (0.03 to 0.16)** |
| Pb | 0.15 (0.08 to 0.23)*** | 0.14 (0.06 to 0.21)** | 0.09 (0.03 to 0.16)* |
| 24-hour SBP | 0.06 (-0.04 to 0.15) | 0.09 (-0.01 to 0.18) | 0.02 (-0.07 to 0.05) |

EDV, end diastolic volume; LVMI, left ventricular mass index; Pb, backward wave pressures; TAC, total arterial compliance; RWT, relative wall thickness; Q, peak aortic blood flow; SBP, systolic blood pressure; SBPc, central aortic systolic blood pressure; SVR, systemic vascular resistance; TAC, total arterial compliance; Zc, aortic characteristic impedance. All relationships are adjusted for age, sex, regular alcohol intake, regular tobacco intake, BMI (except for LVMI-BSA) or body weight (LVMI-ht$^{1.7}$), DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; $^{\dagger}$p<0.05, $^{\dagger\dagger}$p<0.001 versus RWT relationships.

Table 4.3. Relationships (partial r) of hemodynamic factors with left ventricular (LV) mass index (LVMI) and geometric LV remodelling in untreated participants from a community sample in Africa (n=501 and 310 with 24-hr BP).

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | RWT vs |
| Stroke volume | 0.47 (0.40 to 0.53)***††† | 0.26 (0.18 to 0.33)***† | 0.14 (0.06 to 0.22)** |
| Peak aortic Q | 0.17 (0.09 to 0.25)*** | 0.11 (0.03 to 0.19)** | 0.09 (0.01 to 0.17)* |
| EDV | 0.46 (0.39 to 0.52)***††† | 0.29 (0.22 to 0.36)***††† | 0.11 (0.03 to 0.19)* |
| SVR | -0.47 (-0.53 to -0.41)*** ††† | -0.25 (-0.32 to -0.17)***††† | -0.02 (-0.11 to 0.06) |
| Zc | 0.01 (-0.07 to 0.09) | 0.06 (-0.02 to 0.14) | 0.04 (-0.04 to 0.12) |
| TAC | 0.26 (0.18 to 0.33)***††† | 0.10 (0.02 to 0.18)* | 0.03 (-0.05 to 0.11) |
| SBPc | 0.19 (0.11 to 0.28)*** | 0.21 (0.12 to 0.29)*** | 0.09 (0.01 to 0.17)* |
| Pb | 0.24 (0.15 to 0.32)***† | 0.20 (0.12 to 0.29)*** | 0.11 (0.03 to 0.19)* |
| 24-hour SBP | 0.18 (0.06 to 0.28)**† | 0.18 (0.07 to 0.29)** | 0.03 (-0.07 to 0.13) |

See Table 4.2 for abbreviations. All relationships are adjusted for age, sex, regular alcohol intake, regular tobacco intake, BMI (except for LVMI-BSA) or body weight (LVMI-$ht^{1.7}$), DM and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; †p<0.05, ††p<0.005, †††p<0.0005 versus RWT relationships.

Table 4.4. Relationships (partial r) of hemodynamic factors with left ventricular (LV) mass index (LVMI) and geometric LV remodelling in women from a community sample in Africa (n=479 and 288 with 24-hr BP).

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | RWT vs |
| Stroke volume | 0.38 (0.31 to 0.45)***†† | 0.18 (0.09 to 0.25)***† | 0.06 (-0.02 to 0.14) |
| Peak aortic Q | 0.15 (0.07 to 0.24)** | 0.10 (0.02 to 0.18)* | 0.06 (-0.03 to 0.14) |
| EDV | 0.36 (0.29 to 0.31)***†† | 0.18 (0.10 to 0.26)***† | 0.05 (-0.03 to 0.14) |
| SVR | -0.35 (-0.42 to -0.27)***†† | -0.14 (-0.22 to -0.06)**†† | 0.08 (-0.006 to 0.16) |
| Zc | 0.002 (-0.08 to 0.09) | 0.04 (-0.05 to 0.12) | 0.03 (-0.05 to 0.11) |
| TAC | 0.21 (0.13 to 0.29)***† | 0.05 (-0.04 to 0.13) | -0.04 (-0.13 to 0.04) |
| SBPc | 0.16 (0.07 to 0.25)** | 0.14 (0.05 to 0.23)** | 0.10 (0.02 to 0.18)* |
| Pb | 0.14 (0.05 to 0.23)** | 0.12 (0.03 to 0.21)* | 0.09 (0.01 to 0.17)* |
| 24-hour SBP | 0.07 (-0.05 to 0.18) | 0.08 (-0.04 to 0.20) | 0.03 (-0.08 to 0.13) |

See Table 4.2 for abbreviations. All relationships are adjusted for age, regular alcohol intake, regular tobacco intake, BMI (except for LVMI-BSA) or body weight (LVMI-$ht^{1.7}$), DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; †p<0.05, ††p<0.0005 versus RWT relationships.

Table 4.5. Relationships (partial r) of hemodynamic factors with left ventricular (LV) mass index (LVMI) and geometric LV remodelling in men from a community sample in Africa (n=230 and 145 with 24-hr BP).

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | RWT vs |
| Stroke volume | 0.52 (0.42 to 0.60)***†† | 0.33 (0.22 to 0.44)*** | 0.25 (0.13 to 0.36)** |
| Peak aortic Q | 0.20 (0.08 to 0.31)** | 0.13 (0.003 to 0.25)* | 0.24 (0.15 to 0.35)** |
| EDV | 0.55 (0.46 to 0.63)***†† | 0.36 (0.25 to 0.47)***† | 0.23 (0.11 to 0.34)** |
| SVR | -0.52 (-0.60 to -0.42)***††† | -0.31 (-0.42 to -0.20)***†† | -0.09 (-0.21 to 0.04) |
| Zc | -0.04 (-0.16 to 0.09) | 0.05 (-0.08 to 0.17) | -0.14 (-0.26 to -0.01)* |
| TAC | 0.34 (0.23 to 0.45)***†† | 0.17 (0.05 to 0.29)* | 0.10 (-0.02 to 0.22) |
| SBPc | 0.16 (0.03 to 0.29)* | 0.18 (0.05 to 0.31)* | 0.15 (0.03 to 0.27)* |
| Pb | 0.19 (0.06 to 0.32)** | 0.20 (0.07 to 0.32)** | 0.14 (0.01 to 0.26)* |
| 24-hour SBP | 0.14 (-0.03 to 0.30) | 0.18 (0.01 to 0.33)* | 0.03 (-0.13 to 0.18) |

See Table 4.2 for abbreviations. All relationships are adjusted for age, regular alcohol intake, regular tobacco intake, BMI (except for LVMI-BSA) or body weight (LVMI-$ht^{1.7}$), DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; †p<0.05, ††p<0.005, †††p<0.0005 versus RWT relationships.

Table 4.6. Relationships (partial r) of hemodynamic factors with left ventricular (LV) mass index (LVMI) and geometric LV remodelling in hypertensives from a community sample in Africa (n=501 and 310 with 24-hr BP).

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | RWT vs |
| Stroke volume | 0.39 (0.30 to 0.47)***††† | 0.22 (0.13 to 0.32)***† | 0.10 (-0.01 to 0.20) |
| Peak aortic Q | 0.21 (0.11 to 0.30)*** | 0.15 (0.05 to 0.24)** | 0.18 (0.08 to 0.28)** |
| EDV | 0.42 (0.33 to 0.49)***††† | 0.22 (0.12 to 0.31)***† | 0.09 (-0.01 to 0.19) |
| SVR | -0.33 (-0.42 to -0.24)***††† | -0.14 (-0.24 to -0.04)*†† | 0.06 (-0.04 to 0.16) |
| Zc | -0.05 (-0.15 to 0.05) | 0.02 (-0.09 to 0.12) | -0.08 (-0.18 to 0.03) |
| TAC | 0.25 (0.15 to 0.34)***†† | 0.10 (0.01 to 0.20)* | -0.01 (-0.11 to 0.09) |
| SBPc | 0.18 (0.10 to 0.26)*** | 0.20 (0.11 to 0.28)*** | 0.10 (0.01 to 0.20)* |
| Pb | 0.16 (0.07 to 0.24)** | 0.17 (0.08 to 0.25)** | 0.09 (-0.01 to 0.19) |
| 24-hour SBP | 0.07 (-0.06 to 0.20) | 0.10 (-0.03 to 0.22) | 0.001 (-0.13 to 0.13) |

See Table 4.2 for abbreviations. All relationships are adjusted for age, sex, regular alcohol intake, regular tobacco intake, BMI (except for LVMI-BSA) or body weight (LVMI-$ht^{1.7}$), DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; †p<0.05, ††p<0.005, †††p<0.0005 versus RWT relationships.

Table 4.7. Relationships (partial r) of hemodynamic factors with left ventricular (LV) mass index (LVMI) and geometric LV remodelling in normotensives from a community sample in Africa (n=351 and 222 with 24-hour BP).

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | RWT vs |
| Stroke volume | 0.45 (0.38 to 0.53)***††† | 0.23 (0.14 to 0.32)***† | 0.08 (-0.02 to 0.17) |
| Peak aortic Q | 0.15 (0.06 to 0.24)** | 0.10 (0.01 to 0.20)* | 0.03 (-0.07 to 0.12) |
| EDV | 0.43 (0.35 to 0.50)***††† | 0.26 (0.17 to 0.34)***† | 0.08 (-0.02 to 0.17) |
| SVR | -0.50 (-0.57 to -0.43)***††† | -0.27 (-0.35 to -0.18)***†† | -0.02 (-0.11 to 0.08) |
| Zc | 0.01 (-0.09 to 0.10) | 0.04 (-0.05 to 0.14) | 0.05 (-0.04 to 0.15) |
| TAC | 0.30 (0.21 to 0.38)***††† | 0.13 (0.04 to 0.23)* | 0.02 (-0.07 to 0.12) |
| SBPc | 0.21 (0.12 to 0.29)*** | 0.21 (0.13 to 0.29)*** | 0.10 (0.01 to 0.20)* |
| Pb | 0.23 (0.15 to 0.31)***† | 0.18 (0.10 to 0.26)*** | 0.10 (0.01 to 0.20)* |
| 24-hour SBP | 0.18 (0.07 to 0.29)** | 0.14 (0.03 to 0.26)* | 0.03 (-0.08 to 0.15) |

See Table 4.2 for abbreviations. All relationships are adjusted for age, sex, regular alcohol intake, regular tobacco intake, BMI (except for LVMI-BSA) or body weight (LVMI-$ht^{1.7}$), DM and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships; †p<0.05, ††p<0.005, †††p<0.0005 versus RWT relationships.

The lack of these direct relationships between SVR or Zc with LVMI or remodelling and the lack of inverse relationships between TAC and LVMI or remodelling were noted in several subgroups including untreated participants (Table 4.3), women and men (Tables 4.4 and 4.5) and hypertensives and normotensives (Tables 4.6 and 4.7). Importantly, in 89 participants with isolated diastolic hypertension, a form of hypertension where SVR alone is increased, SVR failed to show independent relations with LVMI or RWT (p=0.09 and p=0.10). Although BP variables (SBPc, Pb and 24-hour SBP) were independently associated with both LVMI and RWT (Tables 4.2 to 4.7), the relationships between BP and RWT were not independent of LVMI (data not shown).

*4.4.3 Hemodynamic correlates of categories of LV remodelling*

In keeping with strong independent correlations between volume and flow-dependent hemodynamic factors and LVMI, as well as RWT (Table 4.2), multivariate adjusted EDV, SV (Figures 4.1 to 4.3), and Q (data not shown) were markedly increased in those with both concentric and eccentric LVH. Importantly, no differences were observed in these variables between these two types of LVH (Figures 4.1 to 4.3). Thus, EDV and SV were as strongly and independently associated with the odds of concentric LVH as they were with eccentric LVH (Figure 4.2). Increases in EDV, SV and Q were noted in both women and men with concentric and eccentric LVH (Tables 4.8 and 4.9). Those with concentric LV remodelling without LVH showed no multivariate adjusted increases in volume or flow-dependent hemodynamic factors (EDV, SV or Q) (Figures 4.1 to 4.3, Tables 4.8 and 4.9). With respect to vascular factors, neither eccentric nor concentric LVH showed increases in Zc or SVR, and indeed both showed similar decreases in SVR (Figures 4.1 to 4.3, Tables 4.8 and 4.9). Neither Zc (Figures 4.1 to 4.3, Tables 4.8 and 4.9) nor TAC (Tables 4.8 and 4.9) differed between the groups. Thus, neither Zc and SVR (Figures 4.1 to 4.3), nor TAC (data not shown) were independently associated with concentric or eccentric LVH.

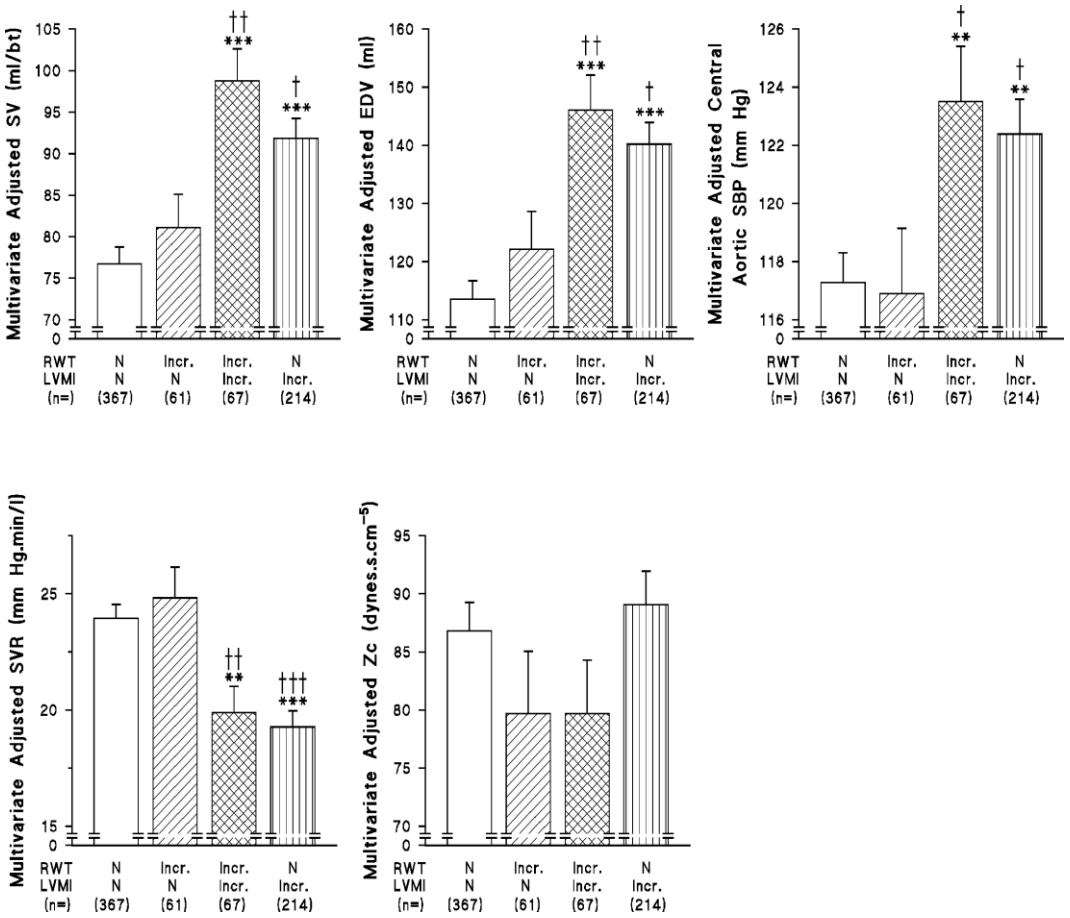


Figure 4.1. Relative impact of volume and pressure load on left ventricular (LV) structural remodelling in a community sample in Africa. Data shown are multivariate adjusted indexes of volume or pressure load or the vascular determinants of pressure load, across categories of LV mass and geometry. EDV, end diastolic volume; LVMI, left ventricular mass index; RWT, relative wall thickness; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; Zc, aortic characteristic impedance.

Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, body mass index, DM, treatment for hypertension and heart rate. **p<0.005, ***p<0.0001 versus normal LV; †p<0.05, ††p<0.005, †††p<0.0005 versus concentric remodelling.

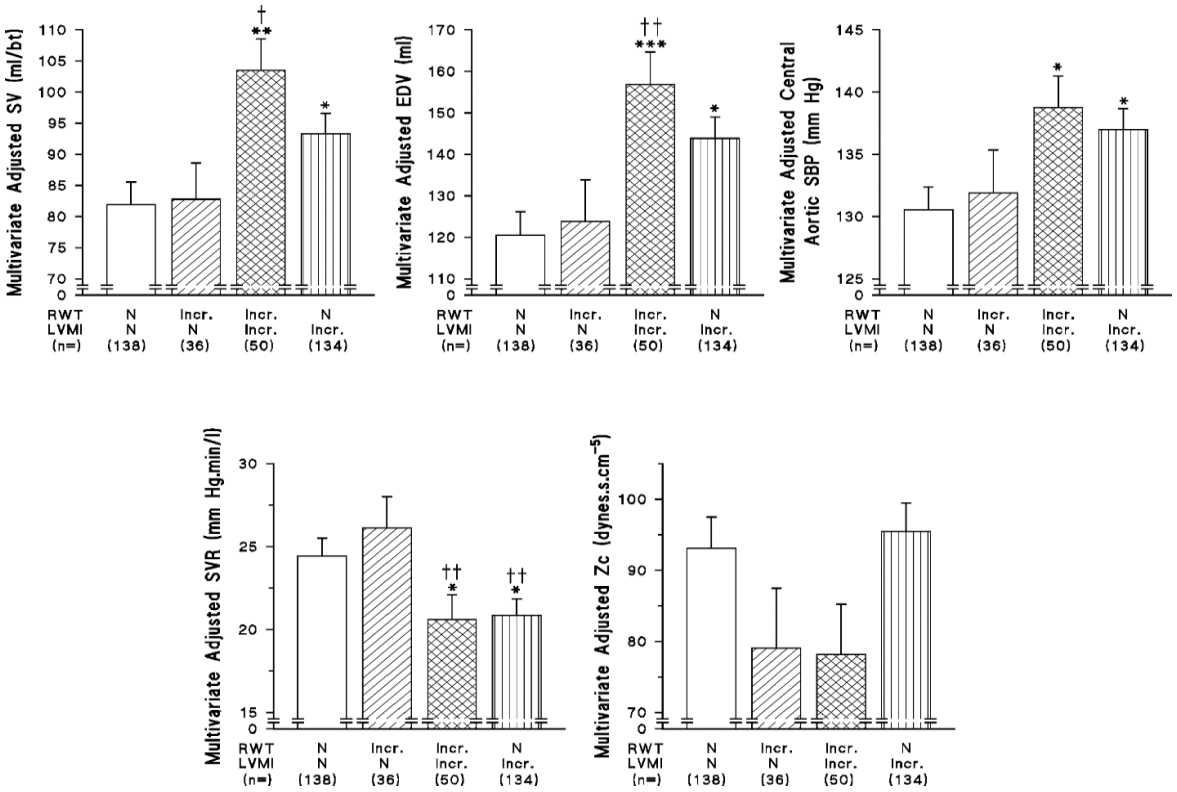


Figure 4.2. Relative impact of volume and pressure load on left ventricular (LV) structural remodelling in hypertensives from a community sample in Africa. Data shown are multivariate adjusted indexes of volume or pressure load or the vascular determinants of pressure load, across categories of LV mass and geometry. EDV, end diastolic volume; LVMI, left ventricular mass index; RWT, relative wall thickness; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; Zc, aortic characteristic impedance. Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, body mass index, DM, treatment for

hypertension and heart rate. **p<0.005, ***p<0.0001 versus normal LV; †p<0.05, ††p<0.005, †††p<0.0005 versus concentric remodelling.

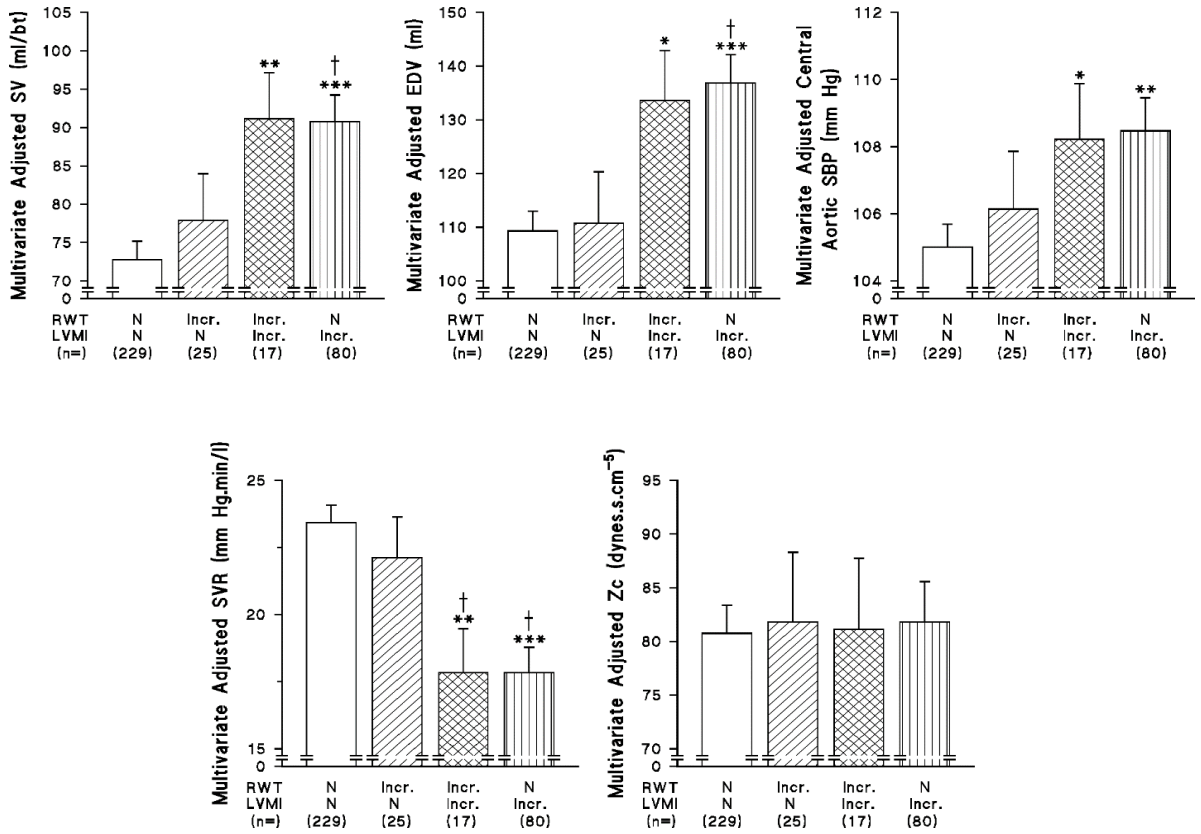


Figure 4.3. Relative impact of volume and pressure load on left ventricular (LV) structural remodelling in normotensives from a community sample in Africa. Data shown are multivariate adjusted indexes of volume or pressure load or the vascular determinants of pressure load, across categories of LV mass and geometry. EDV, end diastolic volume; LVMI, left ventricular mass index; RWT, relative wall thickness; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; Zc, aortic characteristic

impedance. Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, body mass index, DM and heart rate. **p<0.005, ***p<0.0001 versus normal LV; †p<0.05, ††p<0.005, †††p<0.0005 versus concentric remodelling.

Table 4.8. Multivariate adjusted hemodynamic correlates within categories of left ventricular (LV) remodelling in women from a community sample.

| LV mass index (LVMI)→<br>LV geometry→ | Normal<br>Eccentric | Normal<br>Concentric | Increased (LVH)<br>Concentric | Increased (LVH)<br>Eccentric |
|---|---|---|---|---|
| n | 196 | 39 | 56 | 188 |
| Stroke volume (mls/beat) | 73.5±2.7 | 76.6±5.6 | 91.3±4.0** | 87.4±2.5** |
| Peak aortic Q (mls/sec) | 320±13 | 328±27 | 380±19* | 349±12 |
| EDV (mls) | 107±4 | 117±9 | 139±6** | 133±4** |
| SVR (mm Hg.min/l) | 24.0±0.8 | 24.3±1.7 | 20.7±1.2* | 19.9±0.7** |
| Zc (dyne.s.cm$^{-5}$) | 86.1±3.0 | 83.2±6.2 | 82.8±4.4 | 88.0±2.7 |
| TAC (mm Hg/ml) | 2.36±0.96 | 2.51±0.20 | 2.52±0.14 | 2.60±0.09 |
| SBPc (mm Hg) | 115±1 | 116±3 | 123±2* | 121±1* |
| Pb (mm Hg) | 13±0.4 | 12±1 | 14±1* | 14±0.3* |
| 24-hour SBP (mm Hg) | 115±1 | 114±3 | 120±2* | 119±1* |

Data shown are mean±SEM. See Table 3 for abbreviations. Adjustments are for age, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension, and heart rate. *p<0.05, **p<0.001 versus normal LVMI and geometry.

Table 4.9. Multivariate adjusted hemodynamic correlates within categories of left ventricular (LV) remodelling in men from a community sample.

| LV mass index (LVMI)→<br>LV geometry→ | Normal<br>Eccentric | Normal<br>Concentric | Increased (LVH)<br>Concentric | Increased (LVH)<br>Eccentric |
|---|---|---|---|---|
| n | 171 | 22 | 11 | 26 |
| Stroke volume (mls/beat) | 83.9±2.9 | 89.9±7.4 | 115.2±10.6* | 109.5±6.9** |
| Peak aortic Q (mls/sec) | 357±12 | 381±34 | 467±41* | 396±30 |
| EDV (mls) | 127±5 | 133±12 | 167±17* | 164±11* |
| SVR (mm Hg.min/l) | 23.8±0.8 | 25.5±2.1 | 16.2±3.2* | 16.6±1.9** |
| Zc (dyne.s.cm$^{-5}$) | 84.8±3.6 | 72.3±9.9 | 73.3±13.2 | 86.5±8.3 |
| TAC (mm Hg/ml) | 2.68±0.10 | 2.66±0.26 | 2.86±0.44 | 2.92±0.24 |
| SBPc (mm Hg) | 118±1 | 116±3 | 124±5 | 126±3* |
| Pb (mm Hg) | 12±0.4 | 12±1 | 15±1 | 15±1* |
| 24-hour SBP (mm Hg) | 119±1 | 116±3 | 124±4 | 126±2* |

Data shown are mean±SEM. See Table 3 for abbreviations. Adjustments are for age, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension, and heart rate. *p<0.05, **p<0.001 versus normal LVMI and geometry.

However, both concentric and eccentric LVH showed similar striking independent increases in SBPc (Figures 4.1 to 4.3, Tables 4.8 and 4.9), Pb and 24-hour SBP (Tables 4.8 and 4.9) and BP was as strongly and independently associated with the risk of eccentric LVH as it was for concentric LVH (Figure 4.4). Importantly, none of the vascular or pressure-related hemodynamic variables (Zc, SVR, TAC, SBPc, Pb or 24-hour SBP) were increased in those with concentric LV remodelling without LVH as compared to those with a normal LV geometry and mass (Figures 4.1 to 4.3 and Pb or 24-hour SBP not shown). Moreover, neither Zc, SVR, TAC, SBPc, Pb nor 24-hour SBP predicted the presence of LV concentric LV remodelling (Figure 4.4 and Pb or 24-hour SBP in sex-specific groups in Tables 4.8 and 4.9).

*4.4.4 Renin-angiotensin-aldosterone system correlates of LV remodelling*

While increases in aldosterone concentrations and the aldosterone-to-renin ratio (ARR) were positively and independently associated with both LVMI and RWT, renin concentrations were inversely associated with both LVMI and RWT (Table 4.10). Adjustments for LVMI failed to modify relationships between renin or aldosterone system concentrations or ARR and RWT (Table 4.10). Renin concentrations were similarly reduced and aldosterone concentrations and ARR similarly increased in participants with concentric as compared to eccentric LVH (Table 4.11). However, with adjustments for SV or CO, relationships between renin or aldosterone concentrations or ARR and L V structural remodelling were eliminated (data not shown).

*4.4.5 LV systolic functional correlates of LV remodelling*

Left ventricular RWT but not LVMI was independently associated with myocardial systolic function, as determined from FSmid and lateral or septal wall s' or the average thereof (Tables 4.12 to 4.15). This translated into a stepwise decrease in FSmid or s' across incremental quintiles of RWT, while systolic myocardial function remained unchanged across quintiles of LVMI (Figure 4.5). As a consequence of relationships between RWT, but not LVMI and myocardial systolic function, concentric LVH and remodelling, but not eccentric LVH showed a reduced FSmid and myocardial s' (Table 4.16).

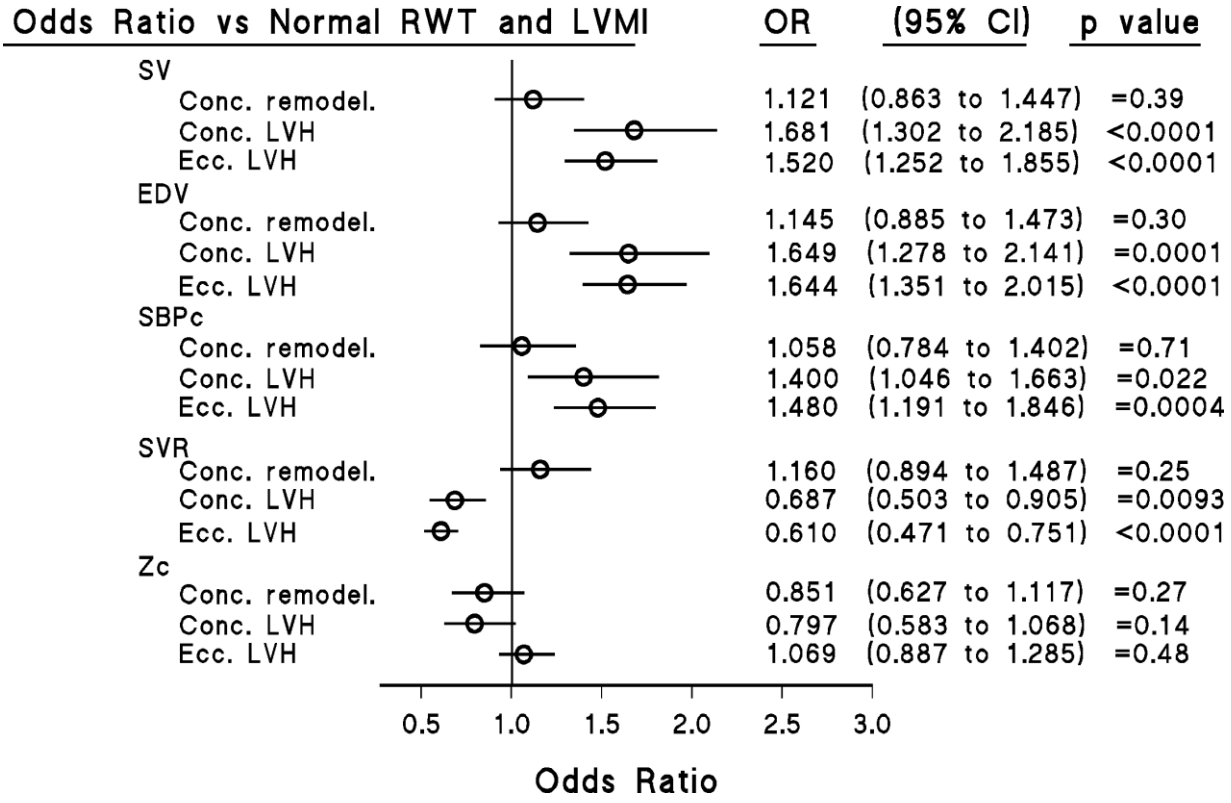


Figure 4.4. Relative impact of volume and pressure load on left ventricular (LV) structural remodelling in a community sample in Africa. Data shown are multivariate adjusted odds of LV mass and geometric remodelling with variations in indexes of volume or pressure overload. See EDV, end diastolic volume; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; RWT, relative wall thickness; SBPc, central aortic systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; Zc, aortic characteristic impedance. Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, body mass index, DM, treatment for hypertension and heart rate. See Table 1 for sample sizes.

Table 4.10. Relationships (partial r) of renin-angiotensin-aldosterone system measurements with left ventricular (LV) mass index (LVMI) and geometric LV remodelling in a community sample in Africa (n=518).

| | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) | Partial r (95% CI) |
|---|---|---|---|---|
| | LVMI-BSA vs | LVMI-$ht^{1.7}$ vs | RWT vs | RWT adjusted for LVMI-$ht^{1.7}$ |
| Renin | -0.015 (-0.087 to 0.058) | -0.035 (-0.107 to 0.038) | -0.007 (-0.080 to 0.066) | -0.006 (-0.079 to 0.066) |
| Aldosterone | -0.034 (-0.106 to 0.039) | -0.055 (-0.127 to 0.017) | -0.011 (-0.097 to 0.075) | 0.009 (-0.077 to 0.095) |
| Aldosterone/renin | 0.018 (-0.056 to 0.091) | 0.032 (-0.041 to 0.106) | 0.041 (-0.032 to 0.114) | 0.043 (-0.030 to 0.116) |

All relationships are adjusted for age, sex, regular alcohol intake, regular tobacco intake, BMI (except for LVMI-BSA) or body weight (LVMI-$ht^{1.7}$), DM, treatment for hypertension and heart rate. *p<0.05, **p<0.005, ***p<0.0001 for significance of relationships.

Table 4.11. Multivariate adjusted renin-angiotensin-aldosterone system concentrations within categories of left ventricular (LV) remodelling.

| LV mass index (LVMI)→ | Normal | Normal | Increased (LVH) | Increased (LVH) |
|---|---|---|---|---|
| LV geometry→ | Eccentric | Concentric | Concentric | Eccentric |
| | 265 | 42 | 50 | 161 |
| Renin (pg/ml) | 46.1±5.4 | 33.2±12.1 | 27.5±8.9 | 29.5±6.0* |
| Aldosterone (ng/dl) | 6.56±0.41 | 6.54±0.87 | 6.55±0.68 | 6.13±0.45 |
| Aldosterone/renin | 0.58±0.11 | 0.55±0.24 | 1.19±0.19** | 0.81±0.13 |

Data shown are mean±SEM. Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension, heart rate and central aortic systolic blood pressure. *p<0.05, **p<0.001 versus normal LVMI and geometry.

Table 4.12. Relationships (partial r) of left ventricular (LV) function with variations in LV mass index (LVMI) or LV relative wall thickness (RWT) in a community sample in Africa (n=709).

| | LVMI-ht$^{1.7}$ Partial r (95% CI) | RWT Partial r (95% CI) | RWT adjusted for LVMI-ht$^{1.7}$ Partial r (95% CI) |
|---|---|---|---|
| LV FSmid | -0.01 (-0.08 to 0.07) | -0.11 (-0.19 to -0.04)**† | -0.12 (-0.20 to -0.05)** |
| LV lateral wall s' | -0.03 (-0.11 to 0.04) | -0.10 (-0.18 to -0.03)** | -0.10 (-0.18 to -0.03)** |
| LV medial wall s' | 0.02 (-0.06 to 0.09) | -0.08 (-0.15 to -0.01)*† | -0.08 (-0.15 to -0.01)* |
| Average LV s' | -0.01 (-0.09 to 0.06) | -0.10 (-0.17 to -0.02)*† | -0.10 (-0.18 to -0.03)** |
| LV lateral wall e' | -0.09 (-0.16 to -0.02)* | -0.08 (-0.15 to -0.01)* | -0.08 (-0.15 to -0.01)* |
| LV medial wall e' | -0.06 (-0.14 to 0.01) | -0.15 (-0.22 to -0.08)***† | -0.15 (-0.22 to -0.08)*** |
| Average LV e' | -0.08 (-0.16 to -0.01)* | -0.12 (-0.19 to -0.05)** | -0.12 (-0.19 to -0.05)** |
| E/e' | 0.12 (0.04 to 0.19)** | 0.10 (0.03 to 0.18)** | 0.09 (0.02 to 0.17)* |

FSmid, LV midwall fractional shortening; s', velocity of myocardial tissue shortening; e', velocity of myocardial tissue lengthening in early diastole; E, transmitral blood flow velocity in early diastole. Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension, heart rate and central aortic systolic blood pressure. RWT is further adjusted for LVMI. *p<0.05, **p<0.005, ***p<0.0005 for significance of relationships; †p<0.05 versus relationship with LVMI.

Table 4.13. Relationships (partial r) of left ventricular (LV) function with variations in LV mass index (LVMI) or LV relative wall thickness (RWT) in untreated participants from a community sample in Africa (n=501).

| | LVMI-ht$^{1.7}$ Partial r (95% CI) | RWT Partial r (95% CI) | RWT adjusted for LVMI Partial r (95% CI) |
|---|---|---|---|
| LV FSmid | 0.05 (-0.04 to 0.13) | -0.12 (-0.20 to -0.03)**†† | -0.14 (-0.22 to -0.05)** |
| LV lateral wall s' | 0.01 (-0.08 to 0.10) | -0.10 (-0.18 to -0.01)*† | -0.11 (-0.19 to -0.02)* |
| LV medial wall s' | 0.03 (-0.06 to 0.12) | -0.08 (-0.17 to 0.01)† | -0.09 (-0.17 to 0.01) |
| Average LV s' | 0.04 (-0.05 to 0.13) | -0.09 (-0.18 to -0.01)*† | -0.10 (-0.18 to -0.01)* |
| LV lateral wall e' | -0.10 (-0.20 to -0.01)* | -0.09 (-0.18 to 0.00)* | -0.10 (-0.18 to -0.01)* |
| LV medial wall e' | -0.07 (-0.17 to 0.02) | -0.11 (-0.20 to -0.03)* | -0.12 (-0.20 to -0.03)* |
| Average LV e' | -0.10 (-0.19 to -0.01)* | -0.11 (-0.19 to -0.02)* | -0.11 (-0.20 to -0.02)* |
| E/e' | 0.12 (0.03 to 0.21)** | 0.10 (0.01 to 0.19)* | 0.10 (0.01 to 0.18)* |

FSend, LV endocardial fractional shortening; FSmid, LV midwall fractional shortening; s', velocity of myocardial tissue shortening; e', velocity of myocardial tissue lengthening in early diastole; E, transmitral blood flow velocity in early diastole. Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, BMI, DM, heart rate and central aortic systolic blood pressure. RWT is further adjusted for LVMI. *p<0.05, **p<0.005 for significance of relationships; †p<0.05, ††p<0.005 versus LVMI relationships.

Table 4.14. Relationships (partial r) of left ventricular (LV) function with variations in LV mass index (LVMI) or LV relative wall thickness (RWT) in women from a community sample in Africa (n=479).

| | LVMI-ht$^{1.7}$ Partial r (95% CI) | RWT Partial r (95% CI) | RWT adjusted for LVMI Partial r (95% CI) |
|---|---|---|---|
| LV FSmid | 0.04 (-0.05 to 0.13) | -0.10 (-0.19 to -0.01)*† | -0.11 (-0.20 to -0.02)* |
| LV lateral wall s' | -0.03 (-0.12 to 0.06) | -0.10 (-0.19 to -0.01)* | -0.10 (-0.19 to -0.01)* |
| LV medial wall s' | 0.04 (-0.05 to 0.13) | -0.10 (-0.18 to -0.01)*† | -0.10 (-0.19 to -0.01)* |
| Average LV s' | 0.01 (-0.09 to 0.09) | -0.11 (-0.20 to -0.02)*† | -0.11 (-0.20 to -0.02)* |
| LV lateral wall e' | -0.11 (-0.20 to -0.01)* | -0.05 (-0.14 to 0.04) | -0.06 (-0.15 to 0.04) |
| LV medial wall e' | -0.07 (-0.16 to 0.03) | -0.16 (-0.24 to -0.07)** | -0.16 (-0.25 to -0.08)** |
| Average LV e' | -0.10 (-0.19 to -0.01)* | -0.11 (-0.20 to -0.02)* | -0.11 (-0.20 to -0.02)* |
| E/e' | 0.10 (0.01 to 0.19)* | 0.10 (0.01 to 0.19)* | 0.10 (0.01 to 0.19)* |

FSend, LV endocardial fractional shortening; FSmid, LV midwall fractional shortening; s', velocity of myocardial tissue shortening; e', velocity of myocardial tissue lengthening in early diastole; E, transmitral blood flow velocity in early diastole. Adjustments are for age, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension, heart rate and central aortic systolic blood pressure. RWT is further adjusted for LVMI. *p<0.05, **p<0.0005 for significance of relationships; †p<0.05 versus LVMI-ht$^{1.7}$ relationships.

Table 4.15. Relationships (partial r) of left ventricular (LV) function with variations in LV mass index (LVMI) or LV relative wall thickness (RWT) in men from a community sample in Africa (n=230).

| | LVMI-$ht^{1.7}$<br>Partial r (95% CI) | RWT<br>Partial r (95% CI) | RWT adjusted for LVMI<br>Partial r (95% CI) |
|---|---|---|---|
| LV FSmid | -0.06 (-0.19 to 0.07) | -0.15 (-0.27 to -0.02)* | -0.13 (-0.26 to -0.01)* |
| LV lateral wall s' | -0.05 (-0.18 to 0.09) | -0.12 (-0.25 to -0.01)* | -0.15 (-0.28 to -0.01)* |
| LV medial wall s' | -0.03 (-0.16 to 0.10) | -0.06 (-0.19 to 0.08) | -0.06 (-0.19 to 0.08) |
| Average LV s' | -0.03 (-0.17 to 0.10) | -0.12 (-0.25 to -0.01)* | -0.14 (-0.27 to -0.01)* |
| LV lateral wall e' | -0.14 (-0.26 to -0.01)* | -0.12 (-0.25 to 0.01) | -0.12 (-0.25 to 0.01) |
| LV medial wall e' | -0.17 (-0.29 to -0.04)* | -0.14 (-0.27 to -0.01)* | -0.12 (-0.25 to 0.01) |
| Average LV e' | -0.14 (-0.27 to -0.01)* | -0.16 (-0.28 to -0.03)* | -0.14 (-0.27 to -0.01)* |
| E/e' | 0.14 (0.01 to 0.27)* | 0.15 (0.02 to 0.28)* | 0.13 (-0.01 to 0.25) |

FSend, LV endocardial fractional shortening; FSmid, LV midwall fractional shortening; s', velocity of myocardial tissue shortening; e', velocity of myocardial tissue lengthening in early diastole; E, transmitral blood flow velocity in early diastole. Adjustments are for age, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension, heart rate and central aortic systolic blood pressure. RWT is further adjusted for LVMI. *$p<0.05$ for significance of relationships.

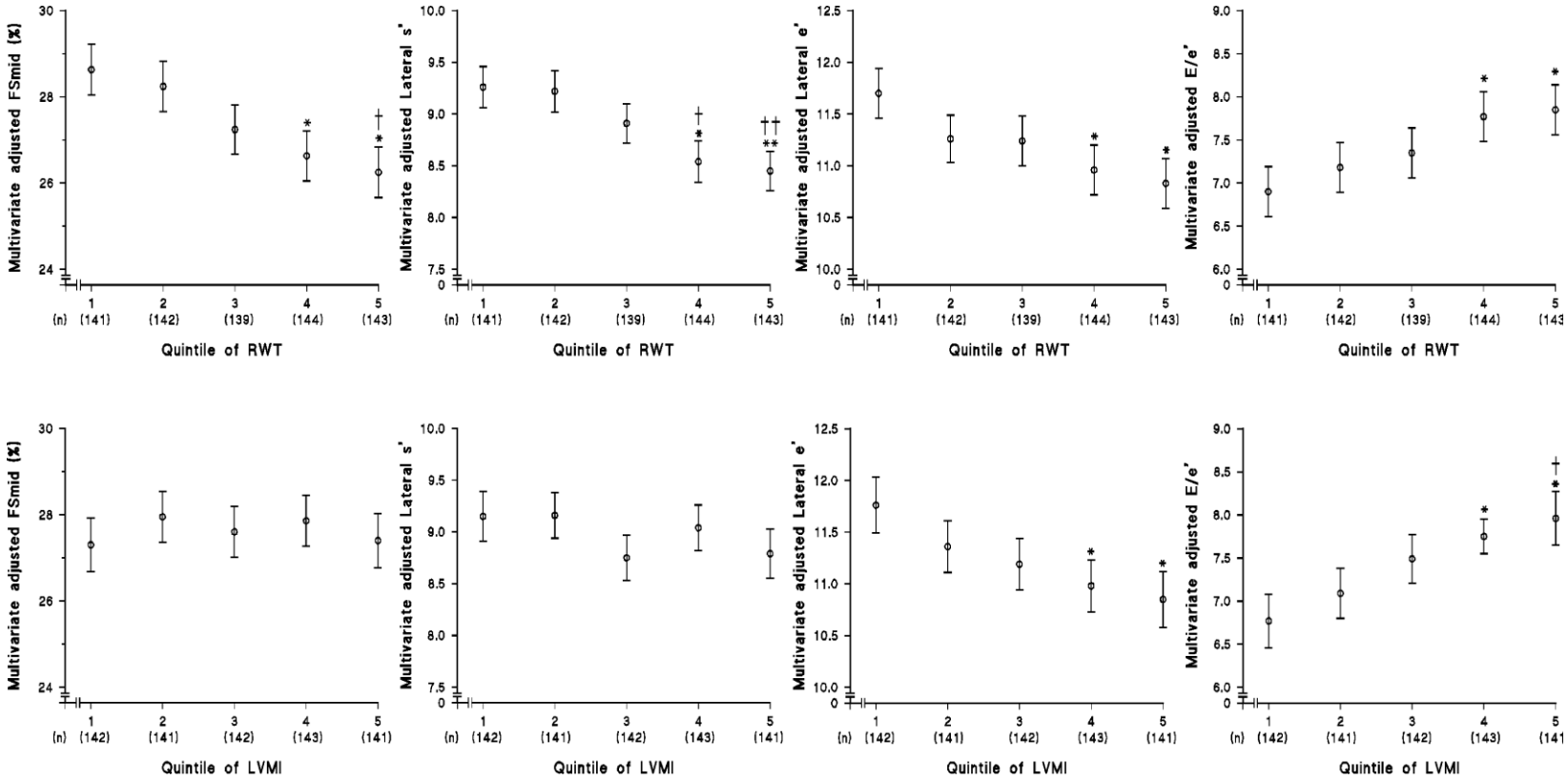


Figure 4.5. Multivariate adjusted left ventricular (LV) systolic chamber and myocardial function across increasing quintiles of LV relative wall thickness (RWT) or LV mass index (LVMI) in a community sample in Africa (n=709). FSmid, midwall fractional shortening; s', velocity of myocardial tissue shortening; e', velocity of myocardial tissue lengthening in early diastole; E, transmitral blood flow velocity in early diastole. Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension, heart rate and central aortic systolic blood pressure. *p<0.05, **p<0.005 versus quintile 1; †p<0.05, ††p<0.005 versus quintile 2.

Table 4.16. Multivariate adjusted functional correlates within categories of left ventricular (LV) remodelling.

| LV mass index (LVMI)→<br>LV geometry→ | Normal<br>Eccentric | Normal<br>Concentric | Increased (LVH)<br>Concentric | Increased (LVH)<br>Eccentric |
|---|---|---|---|---|
| n | 367 | 61 | 67 | 214 |
| LV FSmid (%) | 26.82±0.42 | 23.83±0.90** | 24.55±0.77* | 26.02±0.49 |
| LV lateral wall s' (cm/s) | 9.14±0.16 | 8.28±0.39* | 8.26±0.39* | 8.91±0.21 |
| LV medial wall s' (cm/s) | 8.37±0.14 | 7.85±0.34 | 7.94±0.34 | 8.29±0.18 |
| Average LV s' (cm/s) | 8.69±0.13 | 7.96±0.33* | 7.97±0.32* | 8.64±0.16 |
| LV lateral wall e' (cm/s) | 11.70±0.20 | 11.39±0.48 | 10.80±0.47 | 11.02±0.25* |
| LV medial wall e' (cm/s) | 10.02±0.17 | 8.54±0.40** | 8.96±0.40* | 9.34±0.21* |
| Average LV e' (cm/s) | 10.85±0.16 | 9.97±0.40* | 9.92±0.39* | 10.21±0.21* |
| E/e' | 6.92±0.20 | 7.72±0.50 | 8.04±0.49* | 7.78±0.26* |

Data shown are mean±SEM. See Table 3 for abbreviations. Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension, heart rate and central aortic systolic blood pressure. *p<0.05, **p<0.001 versus normal LVMI and geometry.

*4.4.6 LV diastolic functional correlates of LV remodelling*

In contrast to myocardial systolic function which was only associated with RWT, both LVMI and RWT were independently associated with e' and E/e' (Tables 4.12 to 4.15). This translated into a stepwise decrease in e' and a stepwise increase in E/e' across incremental quintiles of both LVMI and RWT (Figure 4.5). Importantly, however, relationships between RWT and diastolic parameters persisted after adjustments for LVMI (Tables 4.12 to 4.15). Nonetheless, both eccentric and concentric LVH showed similar increases in E/e' and decreases in e' as compared to those with a normal LV (Table 4.16). However, those with a concentric LV geometry but with no LVH showed decreases in e' as compared to those with a normal LV (Table 4.16).

*4.4.7 Renin-angiotensin-aldosterone system correlates of LV function.*

Beyond BP, neither renin or aldosterone concentrations nor the aldosterone-to-renin ratio (ARR) were independently associated with either LV systolic or diastolic function (Table 4.17).

## 4.5 Discussion

The main findings of the present study are as follows: In a community with a high prevalence of volume-dependent, low renin hypertension (Woodiwiss et al 2020, Mmopi et al 2021) we identified the hemodynamic and LV functional correlates of LV remodelling beyond LVMI. In this regard, we show independent and direct (positive) relationships between flow-dependent hemodynamic factors (EDV, SV and peak aortic Q) and both LVMI and RWT. Importantly, both concentric and eccentric LVH were strongly associated with increases in EDV, SV and Q with no differences in these factors noted between the groups. Moreover, we show that neither aortic characteristic impedance (Zc), nor systemic vascular resistance (SVR) were positively associated with either LVMI, RWT or geometric LV remodelling (concentric versus eccentric) in LVH and total arterial compliance (TAC) was not inversely associated with either LVMI, RWT or geometric remodelling in LVH.

Table 4.17. Relationships (partial r) of renin-angiotensin-aldosterone system concentrations with variations in left ventricular function in a community sample in Africa (n=518).

| | Renin<br>Partial r (95% CI) | Aldosterone<br>Partial r (95% CI) | Aldosterone/renin<br>Partial r (95% CI) |
|---|---|---|---|
| LV FSmid | -0.05 (-0.12 to 0.03) | -0.01 (-0.08 to 0.06) | 0.01 (-0.06 to 0.09) |
| LV lateral wall s’ | 0.02 (-0.08 to 0.12) | 0.04 (-0.06 to 0.14) | -0.003 (-0.10 to 0.10) |
| LV medial wall s’ | 0.05 (-0.05 to 0.15) | 0.05 (-0.05 to 0.15) | -0.06 (-0.16 to 0.04) |
| Average LV s’ | 0.03 (-0.06 to 0.14) | 0.05 (-0.05 to 0.15) | -0.03 (-0.13 to 0.07) |
| LV lateral wall e’ | -0.04 (-0.13 to 0.06) | -0.07 (-0.17 to 0.03) | -0.02 (-0.12 to 0.08) |
| LV medial wall e’ | 0.04 (-0.06 to 0.13) | -0.08 (-0.18 to 0.02) | -0.07 (-0.17 to 0.03) |
| Average LV e’ | -0.001 (-0.10 to 0.10) | -0.09 (-0.18 to 0.01) | -0.05 (-0.15 to 0.05) |
| E/e’ | -0.03 (-0.13 to 0.06) | -0.06 (-0.16 to 0.04) | 0.01 (-0.09 to 0.11) |

FSmid, LV midwall fractional shortening; s’, velocity of myocardial tissue shortening; e’, velocity of myocardial tissue lengthening in early diastole; E, transmitral blood flow velocity in early diastole. Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, BMI, DM, treatment for hypertension, heart rate and central aortic systolic blood pressure. *p<0.05, **p<0.005, ***p<0.0005 for significance of relationships.

Furthermore, both concentric and eccentric LVH showed similar increases in several pressures (SBPc, Pb and 24-hour SBP) recognised to be important in the LV remodelling process. In contrast to the lack of hemodynamic factors determining LV geometric remodelling in LVH, we show that while RWT was independently and inversely associated with myocardial systolic function (FSmid and myocardial s'), LVMI was not. Moreover, those with concentric LVH showed a reduced LV systolic myocardial function, while those with eccentric LVH did not. Although RWT was also associated with diastolic functional abnormalities (e' and E/e') beyond LVMI, this failed to distinguish concentric from eccentric LVH. Traditional thought has rendered the view that LV geometric remodelling (RWT) provides insights into the dominant pathophysiological process responsible for LVH. In this regard, while concentric LVH has been viewed as mainly a response to a pressure overload, eccentric LVH is thought to be primarily a response to a volume overload. However, whether the same distinction can be made when LVH occurs in response to a combined impact of both volume and pressure loads, is unknown.

Recent evidence demonstrating a double hemodynamic burden (increases in systemic flow determined by a volume overload as well as associated increases in arterial pressure) responsible for hypertension in a community with prevalent volume-dependent, low renin hypertension (Woodiwiss et al 2020, Mmopi et al 2021) offered a unique opportunity to explore this question. In the present study we show that in this same community (Woodiwiss et al 2020, Mmopi et al 2021), when volume overload is a significant cause of pressure overload, that both hemodynamic loads contribute to LVH and that geometric remodelling is determined by neither pressure nor volume loads beyond LVMI. Thus, although a high prevalence of concentric and eccentric LVH do indeed occur, neither volume nor pressure overload distinguish the geometric remodelling process observed. Under these circumstances, the extent to which underlying systolic myocardial functional abnormalities exist is what distinguishes the geometric LV remodelling process. Indeed, myocardial systolic dysfunction occurs in those with concentric but not eccentric LVH.

These data suggest that in volume-dependent primary hypertension concentric LV geometric remodelling is a compensatory response to maintain systolic chamber function in the face of myocardial dysfunction rather than a response to a dominant pressure rather than volume overload. The present study therefore challenges the current paradigm that LV geometric remodelling provides an index that clearly distinguishes whether a pressure or a volume load primarily determine LVH.

There are several potential implications of the present study. First, as indicated in the aforementioned, in volume-dependent forms of hypertension, LV geometric remodelling cannot be employed as an indicator of the loading condition (volume versus pressure) primarily responsible for LVH. The results of the present study therefore raise the question as to whether the geometric remodelling process indeed enhances risk prediction beyond LVMI in volume-dependent forms of hypertension. As in any population a proportion of individuals may have volume-dependent hypertension, these data may explain why concentric LVH does not always show an enhanced ability to predict risk beyond eccentric LVH and why concentric LV remodelling without LVH often fails to show an increased risk beyond those with a normal LV geometry and mass. Second, the present results also challenge the assumption that concentric LVH progresses to heart failure with a preserved ejection fraction, while eccentric LVH progresses to heart failure with a reduced ejection fraction. Indeed, as indicated from the present study, the primary difference between concentric and eccentric LVH in volume-dependent hypertension is a reduction in myocardial systolic as opposed to diastolic dysfunction.

At present there are no antihypertensive interventions that have a proven ability to reduce systemic blood flow associated with a volume-overload in hypertension. However, regression of LVH can indeed occur with antihypertensive treatment in the present community (Sareli et al 2002). The question therefore arises as to how this may be achieved? Although, as demonstrated in the present study, both concentric and eccentric LVH are strongly determined by a volume overload, the impact of the volume load on LVMI may be through indirect mechanisms. In this regard, as recently demonstrated, Pb is that

factor that largely accounts for variations in LVMI across the full adult lifespan.[17] By increasing systemic flow (Q), the forward travelling pressure wave is augmented, and through Newton's Laws of Motion (inertial effects and for every action there is an equal and opposite reaction) a consequent increase in Pb and hence LVMI will occur. Thus, any intervention that targets central arterial pulsatile pressure load may attenuate the impact of the volume overload on LVMI. Moreover, increases in SV may mediate LVH through an enhanced stroke work (SV x PP). By decreasing PP, the impact of stroke work on LVMI will therefore also be reduced. Thus, targeting systemic blood flow alone may not be necessary to regress LVH in volume-dependent hypertension. However, at present there are no studies that have identified the hemodynamic mechanisms responsible for the regression of LVH with antihypertensive therapy in volume-dependent hypertension. Moreover, the extent to which current therapy results in residual LVH in volume-dependent hypertension has not been identified. Further studies are therefore warranted to identify the best hemodynamic approach to regress LVH in volume-dependent forms of hypertension.

There are several limitations to the present study that warrant consideration. As the present study is cross-sectional in design, no conclusions can be drawn as to whether the relationships noted are indeed cause and effect. Longitudinal studies are therefore warranted to determine whether myocardial systolic functional changes parallel alterations in RWT and whether the development of a volume load precedes the development of both concentric and eccentric LVH. However, as the volume overload begins at an early adult age and progresses across the full adult lifespan (Woodiwiss et al 2020) these studies will require follow-up across the full adult lifespan. Second, whether concentric and eccentric LVH indeed carry the same cardiovascular risk in volume-dependent hypertension requires an outcomes-based study to identify. Third, we did not assess LVMI or EDV using referent (gold-standard) magnetic resonance imaging and hence whether the geometric remodelling process noted in the short axis of the LV reflects similar changes throughout the LV is unknown. However, echocardiography is the most cost-effective screening tool, currently employed for enhancing risk assessment in hypertension, that can identify LV geometry.

Fourth, a significant proportion of participants with LVH were receiving antihypertensive agents. Because of the complex use of different antihypertensive agents and combinations thereof, we were unable to adjust for the use of specific antihypertensive drug classes. However, the consistency of the data in sensitivity analysis conducted in untreated participants supports the main findings of the present study. Last, it is difficult to identify the time of onset of hypertension in any hypertensive, as the time of diagnosis is unlikely to reflect the onset of hypertension unless patients have BP checks very regularly and the transition to treatment is carefully documented. Therefore, we could not account for the duration of hypertension in multivariate adjustments. Consequently, further longitudinal studies, where participants are followed on a regular basis, are required to confirm the present findings.

In conclusion, in the present study we show in a community with prevalent volume-dependent hypertension (Woodiwiss et al 2020), that volume (EDV, SV and Q) overload contributes as much to concentric as it is does to eccentric LVH. Further, we show that pressure overload generated by increases in systemic flow contributes as much to eccentric as it does to concentric LVH, while alterations in vascular factors (SVR, Zc and TAC) play no role in determining the LV geometry in LVH. In contrast to the inability of volume or pressure load to distinguish between concentric versus eccentric LVH, decreases in intrinsic myocardial systolic function (FSmid and myocardial s') were strongly associated with increases in relative wall thickness. Thus, in contrast to current notions, the present study suggests that a concentric LV geometry in hypertensive LVH associated with a volume overload, is primarily a compensatory response to maintain systolic chamber function rather than a response to a pressure rather than a volume load.

# Chapter 5

## Contextual Narrative.

## 5.0 Introduction

With the average lifespan increasing across the globe, there has been a marked shift in the prevalence of diseases from those that contribute to mortality across the early human lifespan (communicable diseases and infant mortality), to disease processes that more commonly affect aging populations (non-communicable diseases). In this regard, heart failure may occur at any age, but more frequently affects middle-aged and older populations. As reviewed in chapter 1 of the present thesis, heart failure effect is largely accounted for by well-established risk factors, of which hypertension explains a significant proportion of the population attributable risk. In this regard, hypertension most commonly occurs in the middle age and in the elderly.

As underscored in chapter 1 of the present thesis, heart failure is a disorder that carries a poor prognosis from the time of initial diagnosis. Although a number of novel and very effective therapeutic approaches to manage heart failure have emerged over the past three decades, these have established therapeutic benefits in heart failure with a reduced ejection fraction. In this regard, in HFpEF, a form of heart failure which accounts for 50% of all heart failure cases, there are no therapies with established benefits. Indeed, despite numerous mechanisms being identified from preclinical studies for the development of LV diastolic dysfunction, the dominant functional abnormality responsible for HFpEF, drug development programs targeting these mechanisms have all resulted in a failure to improve outcomes.

With the consistent failure of clinical trials to show an ability of novel therapies to manage HFpEF, a greater focus on preventing the progression to HFpEF represents a more feasible approach to reducing the health burden of heart failure. Although hypertension can contribute to heart failure with a reduced ejection fraction, hypertension is thought to mainly produce HFpEF. Indeed, aside from age, hypertension is the dominant risk factor responsible for the functional abnormalities in the LV in HFpEF. Although many would view this as the consequence of undetected or poorly managed BP values, as will be discussed in the present chapter, current evidence, including data obtained in the present thesis,

suggests that the problem is more complex. In this regard, it is well-established that heart failure associated with hypertension represents a transition from compensated LVH that occurs in the face of an increased afterload, to LV dysfunction. However, there has been considerable debate as to the haemodynamic factors responsible for this transition process and the alterations in LV structure that account for these effects. In the present thesis, we addressed these questions in a large community sample of African ancestry with a high prevalence of uncontrolled and untreated hypertension. In the present chapter, I will place these results in clinical context. Within the boundaries of the broad limitations of the present study, which will be underscored, I will subsequently suggest how this information may advance our knowledge of the best approach to prevent the development of HFpEF caused by hypertension, this will be done with a particular focus on the unique pathophysiological mechanisms responsible for hypertension in Africa.

## 5.1 Haemodynamic determinants of LV dysfunction in hypertension

Although LV diastolic dysfunction has repeatedly been demonstrated to be an important cause of hypertensive heart failure, there is little understanding of the haemodynamic causes thereof. In this regard, there is still considerable misunderstanding as to the dominant haemodynamic causes of hypertension. Indeed, the most commonly cited haemodynamic determinants of hypertension are those derived from the simple equation (Ohm's Law) that states that Pressure = Flow x Resistance to flow, which in the mammalian cardiovascular system translates into BP being driven by cardiac output and SVR. This equation is indeed the equation that determines steady pressures found in the microvasculature. However, large and medium-sized arteries and the left ventricle face loading conditions determined by PP which influence SBP. As reviewed in chapter 1 of the present thesis, PP and hence SBP is determined by several haemodynamic factors. These include aortic flow, and impedance to flow in early systole (characteristic impedance, Zc), which together determine the pressure generated by forward travelling pressure waves. In this regard, Zc is determined largely by aortic stiffness and diameter. Current evidence supports a dominant role of stiffness-induced increases in Zc in determining PP and SBP

across the adult lifespan (Mitchell et al 2010, Woodiwiss et al 2020). In addition, in black African populations, systemic flow itself has as much of a role to play as Zc in determining BP (Woodiwiss et al 2020). Increases in pressures generated by either aortic flow or Zc generally translate into increases in PP and SBP detected at the peripheral pulse (brachial SBP). The exception is in young adults where a large difference in PP in central versus peripheral arteries may exist (Nichols et al 2011). In this regard, in young adults at a high risk for cardiovascular events, marked increases in aortic stiffness and hence Zc cause increases in aortic pressures that are not detected at the peripheral pulse (Motau et al 2020). Although increases in aortic flow and stiffness are frequently cited causes of increases in BP, the role of reflected (backward travelling) wave pressures (Pb) as causes of increases in PP and SBP is commonly omitted from basic science and clinical texts.

In contrast to increases in flow and Zc, which through forward wave effects largely translate into increases in both central and peripheral PP and SBP over the older adult age, increases in backward travelling pressure waves increase only central arterial PP and SBP. In this regard, the backward travelling pressure wave that appears in central arteries is transmitted outward to peripheral arteries where it appears as a second systolic shoulder with a lower pressure than that generated by the first systolic shoulder (generated by flow and Zc centrally). Thus, increases in backward travelling pressure waves cannot be detected at the peripheral pulse. Importantly, while forward wave pressures and hence brachial PP increases from 50 years of age onward, backward wave pressures increase linearly from below 20 years of age to old age. Thus, unlike increases in forward wave pressures that cause an enhanced brachial PP and hence can be detected at the brachial pulse, there is presently no clinically available measure to detect those with increases in backward wave pressures. However, prior to the work published in ***Hypertension*** (Bello et al 2020) and described in chapter 2 of the present thesis, the role of backward travelling pressure waves as important causes of hypertensive LV diastolic function across the adult age range was uncertain. How has the present thesis contributed to our understanding of the role of backward travelling pressure waves and what are the clinical implications of these findings?

*5.1.1 Backward travelling pressure waves and LV diastolic dysfunction*

Although as reviewed in chapter 1 and highlighted in chapter 2, several studies have demonstrated associations between backward wave pressures and LV diastolic function, in chapter 2 of the present thesis and published in *Hypertension* (Bello et al 2020), in this study, we provide several important insights that advance this knowledge. First, we show that consistent with previous studies performed in middle aged individuals only (Chirinos et al 2013), across the full adult age range, SVR is not a determinant of LV diastolic dysfunction (Bello et al 2020) and hence should not be the primary target for preventing the development of hypertensive HFpEF. Rather we show that a linear age-related increase in backward wave pressures, which determines mainly late systolic load, contributes to a gradual age-related decline in LV diastolic function from an age well before brachial BP begins to increase. This effect is therefore poorly indexed by brachial BP. Second, we show that although age-related increases in arterial stiffness (which increases characteristic impedance, Zc) and Q occur across the adult age range (Woodiwiss et al 2020), they cause LV diastolic function only indirectly through effects mediated by backward wave pressures. In this regard, the pressures generated by the product of Q and Zc, which enhance mainly early systolic load, did not explain age-related decreases in LV diastolic function beyond backward wave pressures (Bello et al 2020). Rather, the pressures generated by the product of Q and Zc only contributed to LV diastolic dysfunction by enhancing backward wave pressures (Bello et al 2020). Thus, the present thesis provides the evidence to show that targeting backward wave pressures should be the primary target to prevent the development of hypertensive HFpEF. There are several implications of the present findings.

*5.1.2 Implications of the importance of backward wave pressures as a cause of LV diastolic dysfunction*

First, as the impact of backward wave pressures are not detected by increases in peripheral BP, the means to detect the adverse effects of the dominant cause of hypertensive LV diastolic dysfunction, is not available in clinical practice. In this regard, the means to detect increases in backward wave pressures is unlikely to occur in the near future

as the devices to determine backward wave effects are far more expensive than oscillometric devices for brachial BP measurement. Thus, alternative measures that index the adverse effects of backward wave pressures on the LV are required. As LVH has always been considered to be the trigger for LV diastolic function, the detection of LVH is one possible index that may assist in identifying the adverse effects of backward wave pressures. In resource-limited and primary care settings, the detection of electrocardiographic LVH is the most logical option. In referral centres in high-income countries, echocardiographic approaches to LVH detection or geometric remodelling, or the measurement of LV diastolic dysfunction are also options. However, as will be discussed in subsequent sections of the present chapter, further work performed in the present thesis challenges the utility of LVH detection or geometric LV remodelling as effective methods of indexing the adverse effects of some common forms of primary hypertension on the LV. What are the implications of the findings presented in chapter 2 for the management of hypertension?

Chapter 2 provides the evidence to indicate that targeting increases in backward wave pressures are essential for the adequate prevention of HFpEF. At this point there is no evidence to show an ability of any specific drug class to target backward wave pressures beyond alternative hemodynamic factors. Thus, backward wave pressures can only be reduced through indirect approaches by decreasing forward wave pressures. In this regard, through inertial effects, a reduction in forward wave pressures will decrease backward wave pressures. Any agent that decreases MAP can reduce forward wave pressures and thus indirectly reduce backward wave pressures. This effect occurs by decreasing distending pressures in the aorta which in-turn will attenuate Zc and hence forward wave pressures. Although enhanced forward wave pressures generally translate into increases in brachial BP, the measurement of brachial PP may be employed as an index for managing backward wave pressures. There are however two important caveats regarding this approach.

First, clinicians should understand that at the age they generally will use PP, as indexed by SBP, to target backward wave pressure with antihypertensive therapy,

approximately half of the damage to the LV causing diastolic dysfunction has occurred. Although some reversal of dysfunction is possible (Tapp et al 2010), reversal of dysfunction is modest at best. Thus, by the age that treatment would be initiated, only half of LV diastolic reserve remains, and hence careful management of increases in backward wave pressures is required. Second, although reductions in brachial BP are the target, increases in backward wave pressures would have occurred in many patients with hypertension while brachial PP remains relatively unchanged. Thus, lower thresholds of brachial SBP are required at an older adult age than what would normally be used in younger patients with hypertension. This would be the only approach that would target patients with increases in backward wave pressures. Indeed, the Sprint Study Group (2021) have clearly demonstrated that intense brachial BP reduction prevents heart failure in hypertensives older than 50 years of age.

## 5.2 The detection of afterload induced LV changes in volume-dependent hypertension

With the understanding that the principal haemodynamic factor that determines hypertensive LV diastolic dysfunction (backward or reflected wave pressures) cannot be adequately evaluated at the brachial pulse, alternative approaches to detecting hypertensive LV effects are required. This is particularly important over the age of 50 years when PP begins to increase, hence indicating similar changes in forward wave pressures (and hence indirectly, also indicating backward wave pressure changes) (Bello et al 2020). By detecting LV changes, this will add to the ability to evaluate the effects of backward wave pressures on LV diastolic function. As indicated in the aforementioned discussion, the most practical approach to detect the adverse effects of backward waves on the LV is through the detection of LVH or the geometric LV changes associated with an increased LV afterload. What has the present thesis contributed toward our understanding of the value of LVH detection or the assessment of LV geometric changes in volume-dependent primary hypertension?

### *5.2.1 LVH detection in volume-dependent primary hypertension*

There is substantial evidence that LVH adds to the ability to predict hypertensive heart failure. In this regard, as reviewed in chapter 1 of the present thesis and further expanded on in chapter 3, the detection of electrocardiographic or echocardiographic LVH is

a well-established index of pressure overload which enhances risk prediction beyond brachial BP measurements. While electrocardiographic measures of LVH are particularly important at enhancing risk prediction in resource-limited and primary care settings, echocardiographic measures of LVH are important for improving risk detection in high-income countries. However, as also highlighted in chapters 1 and 3 of the present thesis, there is now evidence to suggest that LVH is a poor index of the adverse effects of a pressure load (afterload) on LV diastolic dysfunction (Bamaiyi et al 2019). In this regard however, these data (Bamaiyi et al 2019) were obtained in a community sample with documented and unequivocal increases in systemic flow as a primary determinant of hypertension (Woodiwiss et al 2020). As LVH is determined not only by a pressure load (afterload), but also by a volume load (preload-induced increases in stroke volume and hence stroke work), these data (Bamaiyi et al 2019) raise an important question. In this regard, it is possible that in hypertension that is strongly volume-dependent, LVH is an inappropriate index of BP-induced LV diastolic functional abnormalities, because it is so strongly determined by stroke work, which has little impact on LV function. Indeed, as described in chapter 3 and accepted for publication in the *Journal of Hypertension* (Bello et al, in-press), I show that while stroke work determines LVH and not LV diastolic function, BP has no impact on LVH beyond stroke work. Thus, LVH does not account for afterload (BP) effects on LV diastolic function (Bello et al, in-press). These data have several significant clinical implications.

Importantly, the detection of LVH in low-renin hypertension associated with volume-dependent increases in SV is unlikely to add to risk prediction for HFpEF beyond brachial PP. Although it may be argued that the calculation of LVMI depends on end diastolic volume and hence stroke volume, the calculation of LVMI is not determined by peak aortic flow, which was also strongly associated with LVMI. Furthermore, SV and end diastolic volume were strongly and positively rather than inversely associated with relative wall thickness. In this regard, increases in end diastolic volume should decrease rather than increase relative wall thickness if volume-dependent measures influence this calculation. Thus, the

relationships between LVMI and stroke volume or end diastolic volume are likely to be determined by a volume-dependent effect which increases stroke work, rather than simply through end diastolic volume being a factor included in the calculation of LVMI.

The impact of a volume load on the ability of LVMI to predict LV dysfunction applies to several age groups, including those less than 50 years of age and over 50 years of age, but for different reasons. In this regard, while age-dependent increases in SV do occur in those under 50 years of age, this does not translate into increases in forward wave pressures and hence PP until an age when proximal aortic characteristic impedance (Zc) begins to increase (>50 years of age) (Woodiwiss et al 2020). However, these increases in SV before 50 years of age, contribute to marked age-related increases in LV mass index (LVMI). Consequently, increases in LVMI before 50 years of age will not reflect afterload effects on the heart, but rather increases in stroke work. After 50 years of age however, LVMI will reflect both SV and forward wave pressure effects, but these effects will be readily detected at the brachial pulse and hence the ability to predict LV diastolic function will not be beyond brachial PP. Thus, in groups of African ancestry living in Africa, and presumably in other ethnic groups with volume-dependent forms of hypertension, LVMI will have a limited specificity for predicting the development of HFpEF beyond brachial PP.

*5.2.2 Concentric LV remodelling in volume-dependent hypertension*

According to La Place's law as applied to the heart, to reduce wall stress in the face of a pressure overload, the LV wall thickens while the internal diameter remains unchanged. This produces concentric as opposed to eccentric LVH, and the extent of the concentric LV geometric changes is therefore thought to differentiate the impact of pressure from volume overload. Thus, it is possible that in volume-dependent forms of primary hypertension such as that recently described in Africa (Woodiwiss et al 2020), that even if LVH was unable to improve the detection of LV diastolic dysfunction produced by increases in backward wave pressures, that the geometry of the LV may provide an ability to do so. However, as indicated in chapter 4 of the present thesis and accepted for publication in the *American Journal of Hypertension* (Bello et al in-press) in volume-dependent hypertension, concentric

LVH is as strongly determined by systemic flow as eccentric LVH. In addition, BP afterload (including backward wave pressures) is not associated with the LV geometry (Bello et al, in-press). In addition, both concentric and eccentric LVH have similar increases in BP (Bello et al, in-press). Furthermore, in volume-dependent primary hypertension, neither concentric nor eccentric LVH are determined by alternative haemodynamic factors that influence resistance to flow, including SVR, TAC (total arterial compliance) and Zc (Bello et al, in-press). Moreover, although the degree of concentricity of the LV associates with LV diastolic function independent of LV mass, concentric LVH does not show a greater degree of LV diastolic dysfunction than eccentric LVH (Bello et al, in-press). Consequently, it is unlikely that LV geometry will enhance the prediction of HFpEF in volume-dependent primary hypertension. Nonetheless differences in LV geometry were associated with LV systolic myocardial function (both FSmid and s') beyond LVM (Bello et al, in-press), a finding that may explain the geometric remodelling process beyond LVM (the remodelling is to maintain chamber function in the face of a reduced myocardial function). As reductions in LV systolic function could be the consequence of long-standing increases in BP, it is possible that LV geometry could improve on risk prediction in hypertension, albeit that it is unlikely to predict the risk for HFpEF.

**5.3 Further strengths and limitations**

The limitations of each of the aforementioned findings have been underscored in detail in the relevant chapters and these will not be reiterated. However, it is worth highlighting that the findings described in the present thesis are derived from associations observed in a community-based study. As discussed in each chapter, this is an important limitation of the present thesis. Longitudinal observations were not performed, as to conduct such a study would require follow-up of participants over an entire human lifespan. This applies not only to data described in chapter 2 where age-related effects were studied. This also applies to subsequent chapters (3 and 4) as this approach captures the full effect of age-related changes in the various haemodynamic factors evaluated, on LVH and geometry. In this regard, while systemic flow and backward wave pressures increase linearly across

the human lifespan, Zc, TAC and forward wave pressure increase from 50 years of age, the age at which brachial PP begins to increase (Woodiwiss et al, 2020, Bello et al 2020). To study participants over a limited age range, such as would be necessary if longitudinal follow-up was conducted, would only allow for conclusions to be drawn based on the haemodynamic changes observed over this discreet age range. Thus, an important strength of the present thesis is also the cross-sectional study design that evaluates the impact of age-related haemodynamic changes across the full adult lifespan.

**5.4 Future directions**

As indicated, presently there are no therapeutic agents or approaches that are able to specifically target backward wave pressures. Therefore, as described in the present thesis (chapter 2 and Bello et al 2020) and highlighted in section 5.1.2 we suggest that the most appropriate method of prevent HFpEF caused by hypertension is by targeting brachial SBP when PP begins to increase over 50 years of age. Although this is in-line with current recommendations for the management of hypertension anywhere in the world, our data suggest that to achieve normal backward wave pressures, the thresholds for SBP should be as low as possible as brachial BP does not identify those with elevated backward wave pressures. With low brachial SBP thresholds, backward wave pressure effects are likely to be largely eliminated through reductions in forward wave pressures. These low brachial BP thresholds would be more in line with the guidelines for the United States of America (USA), which suggest that BP should be reduced to below 130/80 mm Hg (intense brachial BP reduction) (Whelton et al 2017). Indeed, the benefits conferred by intensive brachial BP reduction are in those over 50 years of age and the main benefits are for heart failure (The Sprint Study Group, 2021). In this regard, current assessments of LVM or geometry will enhance the ability to detect those who will benefit most as long as the hypertension is not volume-dependent and hence confounded by the impact of flow on LVM or geometry. As the presence of a volume overload is generally not assessed, the detection of LVH or geometric LV changes should be assumed to have a low degree of specificity. As long as Doppler indices of LV function are available, this will of course enhance the detection of those most

at risk. However, in primary care and resource-limited settings, only electrocardiographic LVH detection is available. Hence, as suggested by the guidelines for the USA, intense brachial BP reduction is necessary in all of those whose PP and hence SBP increases over 50 years of age. Future studies should therefore be designed to determine whether intensive brachial BP reduction does decrease backward wave pressures to normal levels; and whether the consequent reduction in backward wave pressures produced by intense brachial BP reduction prevents the progression of LV diastolic functional abnormalities. If these criteria are satisfied, then an adequate solution to the current problem of how best to prevent HFpEF caused by hypertension will have been provided.

## 5.5 Conclusions

In conclusion, in the present thesis, the haemodynamic factors that account for age-related decreases in LV diastolic function and the ability of LVM or geometry to detect these effects were evaluated in a group of African ancestry in South Africa. I show that the haemodynamic factor that explains these effects across the full adult lifespan is an age-related increase in backward wave pressures. Importantly, these effects are poorly indexed by brachial BP measurements and because LVM and geometry are so strongly determined by systemic flow in Africa, the adverse effects of backward wave pressures on the LV cannot be better detected with the use of measures of LVM or geometry. These data suggest that it is only with intense brachial SBP reduction from midlife that the linear age-related adverse effects of backward wave pressures on LV diastolic function will be halted in Africa. Until therapy which targets backward wave pressures independent of forward wave pressures is identified, this is the only approach that will prevent the impact of hypertension on HFpEF in Africa.

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# Appendices

Appendix A

Ethics clearance certificates

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Hamza Bello and Elena Libhaber

## HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

## CLEARANCE CERTIFICATE NO. M191086

| | |
|---|---|
| **NAME: (Principal Investigator)** | Dr Hamza Bello and Elena Libhaber |
| **DEPARTMENT:** | School of Physiology<br>Cardiovascular Pathophysiology and Genomics Research Unit |
| **PROJECT TITLE:** | Arteriosclerosis-related aortic dysfunction and the risk of premature cardiovascular disease |
| **DATE CONSIDERED:** | Ad hoc |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | Sub-Study |
| **SUPERVISOR:** | Gavin Norton, Angela Woodiwiss and Vernice Peterson |
| **APPROVED BY:** | Dr C Penny, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 08/11/2019 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

**DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

R14/49 Prof Angela Woodiwiss and Prof Gavin Norton

# HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

## CLEARANCE CERTIFICATE NO. M170401

| | |
|---|---|
| **NAME: (Principal Investigator)** | Prof Angela Woodiwiss and Prof Gavin Norton |
| **DEPARTMENT:** | School of Physiology |
| **PROJECT TITLE:** | Gene Candidates as Determinants of Blood Pressure and Intermediary Phenotypes in the Pathogenesis of Hypertension in Black South Africans |
| **DATE CONSIDERED:** | 26/04/2002 (Initial Approval) |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | Renewal for 5 Years<br>Valid for the Period 01 April 2017 - 30 April 2022<br>Previously M1204108, M070469 and M020472 |
| **SUPERVISOR:** | Prof Angela Woodiwiss |
| **APPROVED BY:** | Professor P Cleaton-Jones, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 07/04/2017 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

**DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

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

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**
R14/49 Prof A/G Woodiwiss/Norton

| | |
|---|---|
| **CLEARANCE CERTIFICATE** | **M1204108** |
| **PROJECT** | Gene Candidates as Determinants of Blood Pressure and Intermediary Phenotypes in Pathogenesis of Hypertension in Black South Africans (Previously M020472 and M070469) |
| **INVESTIGATORS** | Prof A/G Woodiwiss/Norton. |
| **DEPARTMENT** | School of Physiology |
| **DATE CONSIDERED** | Ad hoc |
| **DECISION OF THE COMMITTEE*** | Renewal Approved |

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

**DATE** 2012/05/18 **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.***

**UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG**

Division of the Deputy Registrar (Research)

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**
R14/49 Woodiwiss/Norton

| | |
|---|---|
| **CLEARANCE CERTIFICATE** | **PROTOCOL NUMBER M070469** |
| **PROJECT** | Gene Candidates As Determinants of Blood Pressure and Intermediary Phenotypes in Pathogenesis of Hypertension in Black S Africans |
| **INVESTIGATORS** | Profs A/G Woodiwiss/Norton |
| **DEPARTMENT** | School of Physiology |
| **DATE CONSIDERED** | 07.05.09 |
| **DECISION OF THE COMMITTEE*** | Approved unconditionally (refer M020472) |

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

**DATE** 07.05.09 **CHAIRPERSON** .....
(Professors PE Cleaton-Jones, A Dhai, M Vorster, C Feldman, A Woodiwiss)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Woodiwiss A Prof

---

**DECLARATION OF INVESTIGATOR(S)**

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 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

**UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG**

Division of the Deputy Registrar (Research)

**COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)**
Ref: R14/49 Woodiwiss/Norton et al

**CLEARANCE CERTIFICATE** **PROTOCOL NUMBER** M02-04-72

**PROJECT** Gene Candidates As Determinants of Blood Pressure And Intermediary Phenotypes In Pathogenesis of Hypertension In Black South Africans

**INVESTIGATORS** Prof's AJ/G et al Woodiwiss/Norton et al

**DEPARTMENT** School of Physiology, Wits Medical School

**DATE CONSIDERED** 02-04-26

**DECISION OF THE COMMITTEE** *

Approved unconditionally

UNIVERSITY OF THE WITWATERSRAND
PROF PE CLEATON-JONES
HREC (MEDICAL)
2007-05-09
JOHANNESBURG

This clearance is valid and within the Wits 5 year validity

**DATE** 02-05-14 **CHAIRMAN** ..... (Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c c Supervisor: Prof AJ Woodiwiss
Dept of School of Physiology, Wits Medical School

Works2\ian0015\HumEth97.wdb\M 02-04-72

**DECLARATION OF INVESTIGATOR(S).**

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10001, 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

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## Appendix B

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