

https://dspace.org/

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

Libhaber, Carlos David

2014-04-25
http://hdl.handle.net10539/14589

Downloaded from a DSpace repository. https://dspace.org/

CHAPTER 1

The Transition from Obesity-Induced Left Ventricular Hypertrophy To Abnormalities of Cardiac Function: Current Understanding and Existing Controversies.

1.0 Introduction

The excessive prevalence of obesity in both developed and developing countries is of concern. In the United States of America (USA) earlier reports estimated that~20% of adults were obese (body mass index [BMI] ≥30 kg/m^2) (Mokdad et al 2003, Mokdad et al 2003), whilst in 2004, the prevalence of obesity was noted to be ~31% in men and ~33% in women (Ogden et al 2007). In South Africa, a country which from an economic perspective is considered to be a developing nation, at approximately the turn of the century, in a nationally representative population sample of 13 089 participants, ~29% of men and ~57% of women were noted to be obese (Puoane et al 2002). Although there is no question that weight reduction programmes have proved to be successful, there is evidence to indicate that obesity, once established, is difficult to manage. Indeed, weight reduction programmes seldom result in obese individuals reaching target body weights and the outcome is frequently an inability to maintain decreases in body weight (Latner et al 2002, Perri and Corsica 2002, Anderson et al 2001). The concern regarding the high prevalence of obesity world-wide is based on the evidence that obesity is a major public health risk. What is the current state of this knowledge?

There is substantial evidence to indicate that obesity is associated with a considerable mortality (Allison et al 1997, Calle et al 1999, Heitmann et al 2000, Lahmann et al 2002, McGee 2005, Gu et al 2006, Jee et al 2006, Whitlock et al 2009) and a large component of this is through an increased risk for cardiovascular events (Eckel et al 2002, Klein et al 2004, Poirier P et al 2006, Murphy et al 2006). Indeed, obesity is a risk factor for heart failure (Chen et al 1999, He et al 2001, Johansson et al 2001, Wilhelmsen et al 2001, Kenchaiah et al 2002, 2009, Ingelsson et al 2005a and 2005b, Nicklas et al 2006, Bahrami et al 2008, Spies et al 2009), myocardial infarction (Yusuf et al 2005, Steyn et al 2005) and cerebrovascular events (stroke) (Kurth et al 2002, Suk et al 2003). This increased risk for cardiovascular events is in-part attributed to the association between obesity and classical cardiovascular risk factors, including hypertension, diabetes mellitus, and dyslipidaemia

(Eckel et al 2002, Klein et al 2004). However, there is significant evidence that the adverse effects of obesity on the cardiovascular system are still present even after adjustments for these risk factors. Indeed, the relationships between obesity and the development of heart failure (Chen et al 1999, He et al 2001, Johansson et al 2001, Wilhelmsen et al 2001, Kenchaiah et al 2002, 2009, Ingelsson et al 2005a and 2005b, Nicklas et al 2006, Bahrami et al 2008, Spies et al 2009), myocardial infarction (Yusuf et al 2005, Steyn et al 2005), and stroke (Kurth et al 2002, Suk et al 2003) are noted after adjustments for age, the presence of hypertension, diabetes mellitus and dyslipidaemia. The relationship between measures of adiposity and cardiovascular outcomes independent of traditional cardiovascular risk factors has promoted the concept that obesity could produce damage to key cardiovascular organs that is not necessarily mediated through traditional risk factors. Thus managing hypertension, diabetes mellitus and dyslipidaemias in obesity may be insufficient to prevent obesity-induced increases in cardiovascular risk.

In the present thesis I have conducted a series of studies designed to advance our current understanding of the role of obesity in promoting the transition from left ventricular hypertrophy (LVH) to abnormalities of LV function that could ultimately cause heart failure. Consequently, in the present chapter I will first highlight the need to better understand this question and discuss in more detail the evidence to support the view that obesity is an independent risk factor for the development of heart failure. Second, I will discuss the current evidence to support the view that LVH is an important transition process involved in the evolution of heart failure. Third, I will highlight the evidence to show that obesity is a major determinant of LVH and that this effect has pathophysiological implications. Fourth, I will review the evidence that suggests that obesity is associated with the transition to abnormalities in LV function, and the outstanding evidence with respect to whether these changes are mediated by LVH or abnormalities in LV remodelling, associated haemodynamic factors or alternative changes related to obesity. In this regard, I will highlight the evidence to support or oppose the views that obesity-induced LVH or LV remodelling is a

key determinant of the transition to abnormalities of both diastolic and systolic function of the LV chamber and in so doing underscore the hypotheses developed in the present thesis.

1.1 Heart failure: A need for a better understanding

Heart failure is a condition that from the time of diagnosis, subsequently results in survival rates that are comparable to those of malignancies with the worst possible outcomes (Cowie et al 2000, Stewart et al 2001). Because of the appalling outcomes in patients with heart failure, and the marked burden to health care systems and patients alike produced by heart failure, over the past three-to-four decades there has been a considerable number of studies that have been performed to attempt to improve the current situation.

The past three-to-four decades have been highly successful with respect to research into an understanding of the pathophysiological mechanisms responsible for the progressive decline in cardiac function in heart failure, once heart failure is established. The identification of these mechanisms has culminated in a number of novel therapeutic approaches including the use of blockers of the renin-angiotensin-aldosterone system and β-blockers (Hunt et al 2001). However, in comparison to the success achieved with studies evaluating the mechanisms of the progression of heart failure once it is established, research into the mechanisms responsible for the development of heart failure has been comparatively less successful. In this regard there are still many aspects of heart failure and causes of heart failure where the pathophysiological mechanisms still require further elucidation.

Identifying the pathophysiological mechanisms responsible for the development of heart failure is particularly important in developing countries, such as South Africa. Indeed, a recent clinical audit conducted in a developing community in South Africa, indicates that the burden of cardiovascular disease in a hospital setting appears to be through hospitalizations or referrals for heart failure (Sliwa et al 2008, Stewart et al 2008). An important question that emerges from these data is whether this apparently high prevalence of heart failure in hospital settings in emerging communities (Sliwa et al 2008, Stewart et al 2008) represents

the outcomes of a failed health care system in general, or a high prevalence of disease processes the pathophysiology of which is uncertain. One important question is whether the high prevalence of obesity in these communities accounts for a significant burden of heart failure?

1.2 Excess adiposity is associated with heart failure independent of conventional cardiovascular risk factors.

As alluded to in the aforementioned discussion, over the past decade, a nested case-control study and a number of prospective studies have demonstrated an independent relationship between the degree of adiposity and the development of heart failure (Chen et al 1999, He et al 2001, Johansson et al 2001, Wilhelmsen et al 2001, Kenchaiah et al 2002, 2009, Ingelsson et al 2005a and 2005b, Nicklas et al 2006, Bahrami et al 2008, Spies et al 2009). This relationship has been demonstrated in the general population (He et al 2001, Kenchaiah et al 2002 Ingelsson[b] et al 2005, Bahrami et al 2008), in the middle-aged (Ingelsson[a] et al 2005), in the elderly (Chen et al 1999, Nicklas et al 2006), in men (Wilhelmsen et al 2001, Ingelsson[b] 2005), in women (He et al 2001), in general practice (Johansson et al 2001), in physicians (Kenchaiah et al 2009) and in persons with established coronary artery disease (Spies et al 2009).

As compared to referent BMI between 20 and 25 kg/m^2 (normal) a BMI of between 25 and 30 kg/m^2 (overweight) may increase the risk of heart failure by 39-49% (Bahrami et al 2008, Kenchaiah et al 2009) and a BMI greater than or equal to 30 kg/m^2 (obese) increases the risk of heart failure by 83-180% independent of conventional cardiovascular risk factors (Johansson et al 2001, Kenchaiah et al 2002, Bahrami et al 2008, Kenchaiah et al 2009). In one study however, no increased risk for heart failure was noted in persons with a BMI of between 25 and 30 kg/m^2 (overweight) in a general practice setting (Johansson et al 2001). Moreover, in one study (Spies et al 2009), but not in other studies (Ingelsson[b] et al 2005, Nicklas et al 2006) the adipose tissue-heart failure relationship was better predicted by the

use of indices of adiposity that reflect an accumulation of fat in central (abdominal) stores, such as waist circumference or waist-to-hip ratio, than indices of general adiposity, such as BMI. Depending on the study population and the study design, the independent risk for heart failure in people whom are overweight or obese is quantitatively comparable with the impact of for example the presence of hypertension, or diabetes mellitus in these same studies.

Although the relationship between excess adiposity and the development of heart failure is modified by adjustments for conventional cardiovascular risk factors, including hypertension, diabetes mellitus and cholesterol concentrations as well as with adjustments for coronary events, the impact of these adjustments is surprisingly modest. Indeed, considering overweight and obese persons overall, the percentage risk for heart failure is diminished by only 1-13% with these adjustments (He et al 2001, Ingelsson et al 2005a, 2005b, Nicklas et al 2006, Spies et al 2009) and by only 55% in obese individuals in a study in which obesity increased the risk for heart failure by 180% (Kenchaiah et al 2009). Thus, although there is no question that to prevent overweight/obesity-induced heart failure, targeting modifiable cardiovascular risk factors with lifestyle interventions and medication is an essential approach, the large residual risk for heart failure after adjustments for conventional cardiovascular risk factors indicates that this may not be the most appropriate solution. Better understanding the mechanisms by which excess adiposity contributes toward heart failure may shed light on more effective therapeutic approaches other than weight loss *per se*.

2.0 Transition from cardiac hypertrophy to heart failure: What is the evidence?

As will be highlighted in subsequent discussion, at a population level, obesity contributes the most to variations in left ventricular mass (LVM) indexed to allometric signals to height. The concept that LVH preceeds the development of cardiac dysfunction and subsequently heart failure has been well documented. However, the debate as to whether LVH is a compensatory change or whether LVH causes decompensation has still not been

completely resolved. Assuming that LVH is involved in the pathophysiology of heart failure, as obesity causes LVH, it is also possible that obesity-induced LVH is involved in the pathophysiology of obesity-related heart failure. Hence, before discussing the impact of obesity on LVH and abnormalities in LV function, I will first highlight the evidence to indicate that LVH may be involved in the transition to LV dysfunction.

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, these 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 heart failure. Therefore, the role of LVH as a cause of heart failure remains controversial. The following section will highlight the evidence both for and against LVH as a pathophysiological process responsible for heart failure. However, first I will discuss the potential theories that suggest that LVH could promote the development of cardiac decompensation and heart failure.

2.1 Potential mechanisms through which left ventricular hypertrophy may promote cardiac decompensation.

The miriad of potential mechanisms that may be responsible for the transition from LVH to LV dysfunction have been extensively reviewed on a number of occassions, with a more recent review on pressure-overload hypertrophy eminating from Frohlich et al (2010). A complete elaboration of all of these mechanisms goes beyond the scope of the present thesis. In brief, however, because of a shift in substrate utilisation from fatty acids to carbohydrates, the hypertrophied heart is an energy-compromised organ with diminished adenosine triphosphate (ATP) production; and hence is sensitive to lipotoxicity and contractile dysfunction through the accumulation of intracellular fatty acids (Bugger et al

2010). In LVH re-expression of the cardiomyocyte fetal gene programme occurs which includes repression of genes important for myocardial relaxation (e.g SERCA2) and contraction (e.g. α myosin heavy chain) and overexpression of genes responsible for prgrammed cell death (apoptotic pathways). Activation of specific protein kinases in LVH may induce apoptosis (Liu et al 2000, Wang et al 1998) with an ensuing decline in intrinsic myocardial contractility and myocardial systolic function (Brooks et al 1997). Not only is there excessive apoptosis in LVH, but also an increase in cardiomyocyte autophagy. Moreover, LVH may diminish LV systolic function as a consequence of chamber dilatation which develops subsequent to reparative interstitial changes (Bing et al 1995, Norton et al 2002, Tsotetsi et al 2001) or apoptosis (Liu et al 2000, Wang et al 1998). Through a global increase in collagen gene expression, LVH is associated with an increase in LV stiffness. Furthermore, reparative myocardial fibrosis, induced by tissue necrosis (Tsotetsi et al 2001), or reactive fibrosis (Brilla et al 1996, Weber et al 1990), may promote increases in LV stiffness (Conrad et al 1995) and alterations in the cross-linked properties of myocardial collagen may also increase myocardial stiffness (Norton et al 1997). Thus, a host of potential pathophysiological changes may occur in LVH that may explain a transition from compensated to decompensated LVH. What is the evidence therefore to support a causal role of LVH in the pathophysiology of LV dysfunction?

2.2 What evidence supports or opposes the theory that left ventricular hypertrophy is causally related to cardiac decompensation?

Few studies that have examined the possible causal role of LVH in cardiac decompensation have been able to segregate the adverse effects of blood pressure (BP) or LV load on cardiac function from those potentially mediated by the presence of LVH *per se*. Although not extensive, there is nevertheless some pre-clinical and clinical evidence that provide insights into this question. These pre-clinical and clinical findings either supporting or

refuting the view that LVH mediates cardiac decompensation will be reviewed in the following section.

2.2.1 Pre-clinical evidence supporting or opposing the theory that left ventricular hypertrophy is causally related to cardiac decompensation.

There are a number of pre-clinical studies that have demonstrated that the development of LVH is associated with LV dysfunction (Hernandez et al 2013, Frohlich et al 2010, Dodd et al 2012, Reutter et al 2011, Brooks et al 2010) and that regression of LVH is associated with improvements in LV systolic or diastolic function (Hernandez et al 2013, Frohlich et al 2010, Dodd et al 2012, Reutter et al 2011, Brooks et al 2009) However, as previously indicated, with the exception of a few studies, none of these studies have been able to segregate the adverse effects of BP or LV load on the heart from those potentially produced by LVH *per se*. Nevertheless, revealing insights as to whether LVH *per se* could be causally related to the progression to heart failure have been provided by a few pre-clinical studies. In one pre-clinical study the striking outcome was the finding that genetic modifications targeting molecules that influence sympathetic nervous system activation, that reduce the LV hypertrophic response to a pressure overload state in mice, attenuate the development of LV decompensation (Esposito et al 2002). A bold interpretation of this study (Esposito et al 2002) could be that an attenuation of pressure overload-induced increases in LVM prevented the transition to cardiac decompensation. Alternatively, these data may also be interpreted as an indication that the genetic variations themselves, which reduced sympathetic nervous system activity, were protective. Irrespective of the cause however, these data (Esposito et al 2002) dispel the notion that LVH is a necessary compensatory response to maintain cardiac function in pressure overload states. However, they do not necessarily imply a deleterious effect of LVH *per se*.

In contrast to evidence from pre-clinical studies that suggests that LVH may promote the transition to cardiac decompensation, there are pre-clinical studies which do not support this standpoint. Indeed, in rats, following chronic pressure overload, the extent of LVH may be equivalent in animals with as opposed to those without evidence of left heart failure (Norton et al 2002). Thus I must question whether LVH independently governs the progression to cardiac decompensation. Nevertheless the authors of that study (Norton et al 2002) could not rule out the possibility that those animals identified as having compensated LVH may have been in an earlier phase of LV decompensation. Indeed, in that study myocardial systolic function in rats without heart failure was diminished (Norton et al 2002).

Further evidence opposing a role of LVH as a critical mediator in the development of cardiac decompensation comes from data which indicate that the progression from compensated LVH to either diastolic decompensation (Norton et al 1997) or systolic decompensation and cardiac dilatation (Tsotetsi et al 2001) can be attenuated by antihypertensive agents that do not regress LVH. If LVH was a critical mediator in the transition to cardiac decompensation, we would expect that in the presence of persistent LVH, animals would develop some degree of either diastolic (Norton et al 1997) or systolic (Tsotetsi et al 2001) dysfunction in comparison to animals which did not receive antihypertensive therapy. However, the authors of these studies (Norton et al 1997, Tsotetsi et al 2001) could not exclude the possibility that LVH in the presence of an elevated BP promotes cardiac decompensation. Nevertheless, at the very least, these studies suggest that LVH is not a change which in its own right triggers the transition to cardiac decompensation (Norton et al 1997, Tsotetsi et al 2001).

2.2.2 Clinical evidence supporting or opposing the theory that left ventricular hypertrophy is causally related to cardiac decompensation.

Is there clinical evidence to either support or dispel the notion that LVH promotes LV decompensation? In keeping with the classical tenet that LVH is a compensatory response

to increases in LV load and myocardial systolic dysfunction, an increased LV mass (LVM) is associated with an unchanged LV chamber systolic function as indexed by ejection fraction (EF) (Aurigemma et al 1995, de Simone[b] et al 1994, Shimizu et al 1991). Moreover, LVH may even be associated with an enhanced EF for that predicted by wall stress (Hartford et al 1985). Thus, earlier studies favour LVH being a compensatory change rather than a pathophysiological process responsible for cardiac decompensation.

There are few longitudinal studies which provide insights into the significance of the relationship between LVM and cardiac decompensation. In this regard, in a cohort of the Cardiovascular Health Study (CHS) which was followed for approximately five years, (Drazner et al 2004), independent of traditional risk factors, including conventional BP, LVH was associated with the development of a decreased LV EF. Since a reduced LV EF in asymptomatic patients is associated with the subsequent development of heart failure (Wang et al 2003), it is possible that an increase in LV mass may be a critical pathophysiological mechanism which drives the transition to heart failure. However, intervention studies demonstrating that regression of LVH with therapy is associated with an improved LV systolic chamber function would be required to put this question to rest. What have intervention studies demonstrated?

There are few intervention studies that provide insights into the pathophysiological role of the relationship between LVH and cardiac decompensation. In keeping with the classical tenet that LVH is a compensatory response to increases in LV load and myocardial systolic dysfunction, on-treatment decreases in LVM (Perlini et al 2001) have been shown to be associated with an unchanged LV EF. Whether a significant number of patients had systolic chamber dysfunction to begin with in this study (Perlini et al 2001) may however be questioned. Further insights may nevertheless be gained from the Losartan Intervention For Endpoint reduction (LIFE) study. The multicentre LIFE study evaluated a large sample of hypertensive patients with electrocardiographic evidence of LVH. The LIFE study found a greater regression of LVH in the patient group treated with an angiotensin II receptor blocker in combination with other antihypertensive agents, as compared to the patient group

receiving a β-adrenoreceptor blocker together with other antihypertensive agents (Okin et al 2003). As compared to the β-adrenoreceptor blocker-treated group, patients receiving the angiotensin II receptor blocker experienced a greater reduction in overall cardiovascular mortality (Dahlof et al 2002). Surprisingly though, the secondary end-point of heart failure was not reduced to a greater extent in the angiotensin II receptor blocker treated group (Dahlof et al 2002). Moreover, in the echocardiographic subgroup of the LIFE study, on-treatment decreases in LVM were related to reductions rather than increases in indices of LV systolic chamber function, despite improvements in indices of myocardial systolic function (Wachtell et al 2002). Thus, the LIFE Study provides contradictory evidence for a pathophysiological role for LVH as a cause of cardiac decompensation.

Are there additional clinical intervention studies that provide some insight into the role of LVH as a causal factor in the development of heart failure? Notably, in the Heart Outcomes Prevention Evaluation (HOPE) trial, angiotensin-converting enzyme inhibition both reduced LVM and improved LV function beyond BP control (Lonn et al 2004), providing some additional evidence that LVH may be causally related to LV dysfunction.

One explanation for the variable relationships between LVM or LVM index (LVMI) and LV systolic chamber function is that absolute LVM and LVMI may incorporate a component of LVH considered to be compensatory in nature, whilst also reflecting a component of LVH that contributes to systolic decompensation of the LV chamber. What are the possible factors that determine whether LVH is a decompensatory response?

2.2.3 Inappropriate left ventricular hypertrophy may explain the transition from compensated to decomensated left ventricular hypertrophy.

One proposal for the transition from compensated LVH to LV systolic chamber decompensation is that LVH in-keeping with work load (i.e. stroke work=blood pressure x stroke volume) is compensatory, whilst that exceeding workload (i.e. “inappropriate” LVM [LVM_{inappr}]) (de Simone et al 1998) contributes toward decompensation. Indeed a number of

studies have demonstrated an inverse relationship between LVM_{inappr} and LV systolic chamber 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). However, whether LVM_{inappr} is associated with a reduced systolic chamber function independent of and more strongly than absolute or indexed LVM is uncertain. Some prior studies conducted in select clinical samples have demonstrated inverse correlations between LV systolic chamber function and both absolute LVM as well as LVM_{inappr} (Palmieri et al 1999, Palmieri et al 2001) and in one these studies LVM was equally as strongly inversely correlated with EF as LVM_{inappr} (Palmieri et al 2001). This finding is at odds with the notion that it is only LVM beyond stroke work that explains decompensation. Thus, whether inverse relationships between LVM_{inappr} and EF are independent of absolute LVM is unclear. Moreover, prior relationships between LVM_{inappr} and LV systolic chamber function were demonstrated in cross-sectional studies (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). Conclusions regarding cause and effect cannot be drawn from cross-sectional studies. Indeed, relationships between LVM_{inappr} and LV systolic chamber function may reflect residual confounding effects or compensatory increases in LVM as a consequence of systolic dysfunction (reverse causality). Although one previous study has reported that on-treatment regression but not persistence of LVM_{inappr} is associated with an improved EF (Muiesan et al 2007), whether increases in EF in the participants showing regression of LVM_{inappr} in that study were independent of or stronger than changes in LVM or LVMI is uncertain. Thus further work is required to assess these relationships.

In the present thesis, as I noted that the strongest determinant of LVM_{inappr} was obesity, I performed several studies (community-based and prospective intervention studies) to further evaluate the hypothesis that inappropriate LVH rather than LVM or LVM index accounts for EF. In this regard I have provided substantially more evidence to indicate that inverse LVM_{inappr} and LV systolic chamber function relations are indeed likely to be beyond LVM or LVMI and that these relations may be accounted for by increases in LVM_{inappr} rather

than residual confounding effects or reverse causality. In one of these studies I evaluated the independent relationship between LVM_{inappr} and EF independent of LVM or LVM index in a large randomly selected community-based study. In a secondary study I evaluated the relationship between antihypertensive treatment-induced decreases in LVM_{inappr} and increases in EF independent of LVM or LVM index. The hypotheses advanced will be described later in this chapter and the details of the studies are given in chapters 4 and 5. Importantly, these studies have been published in-part in the journals *Hypertension* and *J Hypertens* (Libhaber et al 2013, Woodiwiss and Libhaber et al 2012).

2.2.4 Left ventricular geometry may explain the transition from compensated to decompensated left ventricular hypertrophy

When reflecting on the role of LVH as a possible cause of LV dysfunction, it is also important to consider the LV remodelling process that coexists with LVH. In this regard, it is now well accepted that heart failure may occur as a consequence of a reduced or preserved EF and that therapy may have differential effects on mortality in these two different groups of patients (Borlaug and Redfield 2011, Holland et al 2011). Patients with a reduced EF generally have associated eccentric LV remodelling (increases in chamber volumes that exceed increases in wall thickness), whilst patients with a preserved EF are thought to have abnormalities of diastolic function produced in-part by excessive LV wall thickness (concentric LV remodelling) (Zile et al 2008). Indeed, concentric LV remodelling is strongly associated with a reduced LV early-to-late (atrial) (E/A) transmitral velocity, and an increase in the relationship between measures of myocardial tissue relaxation in the early phase of diastole (e') and E (E/e'), or alternative indexes of LV diastolic function (Chahal et al 2010, Schillaci et al 2002, Fischer et al 2003). As decreases in E/A reflect a shift in LV filling from early to late diastole, this index is thought to reflect both an impaired relaxation of the LV and changes in left atrial driving pressures, alterations which could occur as a consequence of changes in either active processes in the myocardium or through a stiffer LV. In addition, as

e' is thought to reflect only changes in LV relaxation, an increase in E/e' is hypothesised to index increases in left atrial driving pressures only and hence filling pressures in the LV (Paulus et al 2007). As concentric LV remodelling is strongly associated with abnormalities of LV diastolic function (Chahal et al 2010, Schillaci et al 2002, Fischer et al 2003), many of the controversies associated with the possible role of LVH as a cause of heart failure or a reduced EF may in-part be associated with the original definitions of heart failure or cardiac decompensation. In this regard, although subsequently modified, these original definitions did not recognise heart failure with a preserved EF as a form of heart failure. Moreover, these original definitions failed to acknowledge cardiac decompensation as consisting of two possible forms, either diastolic or systolic decompensation, either of which may progress to heart failure. In the present thesis I have therefore carefully considered the role of both concentric and eccentric remodelling as determinants of obesity-induced diastolic and systolic LV decompensation. Obviously the important question that requires answering when discussing the role of obesity-induced LVH or remodelling in the pathophysiology of the transition to LV dysfunction, is to what extent does obesity contribute toward LVH and either concentric or eccentric LV remodelling?

3.0 Obesity is a major determinant of left ventricular hypertrophy

A strong relationship between body size and LVM is supported by a number of studies with large sample sizes (Lauer et al 1991, Lauer et al 1992, de Simone et al 1992, de Simone[a] et al 1994, Gottdiener et al 1994, Urbina et al 1995, Gardin et al 1995, Sherif et al 2000, Lorber et al 2003, Fox et al 2004). Importantly, even in large cohorts of mild-to-moderate hypertensive patients, BMI is the strongest predictor of LVM (Lauer et al 1992, Gottdiener et al 1994). The effects of body size may be through either the impact of adiposity and muscularity, effects which are accounted for by indexing LVM for body surface area, or simply by growth effects, which are in-turn, accounted for by indexing LVM for height to appropriate allometric signals (growth signals). The fact that a bigger body size, irrespective

of the reason (muscularity, obesity or growth) results in an increased LVM obviously raises the question as to whether obesity-induced LVH is truly pathological or a necessary compensatory change to generate an increased blood flow (cardiac output) for a larger body size.

In support of a pathological role for obesity-induced LVH, LVM indices that incorporate the impact of adiposity on LVM (those indexing LVM for allometric signals of height) are associated with a higher proportion of incident cardiovascular events than are LVM indices that discount the impact of adiposity on LVM (those indexing LVM for body surface area) (de Simone et al 2005). Consequently, unlike normal growth effects on LVM which are physiological in nature, obesity-induced LVH is currently considered to be of pathophysiological significance. However, no study has produced evidence to indicate that obesity-induced LVH is causally related to heart failure. Hence, there is insufficient evidence to draw a firm conclusion that obesity-induced LVH is indeed a pathophysiological process. Is there alternative evidence to support a pathophysiological role for obesity-induced LVH?

Importantly, recent evidence suggests that obesity enhances the impact of blood pressure (BP) on LVM (Avelar et al 2007, Norton et al 2009) potentially through the adverse effects of leptin (Norton et al 2009). As BP effects on the heart are generally considered to be of pathological relevance, these data may provide further evidence to support a view that obesity effects on LVM are of pathophysiological and not just physiological significance. It is nevertheless important to note that previous studies had failed to show such interactions (Fox et al 2004, Lauer et al 1992). However, in these prior studies, either participants with a narrow range of BP levels were evaluated due to the exclusion of treated participants (Lauer et al 1992), or analysis was conducted in a sample in whom ~50% of participants were receiving antihypertensive treatment (Fox et al 2004).

Perhaps the strongest evidence in support of a pathophysiological role for obesity-induced LVH, is now the considerable data obtained from preclinical and clinical studies to suggest that obesity-induced LVH is indeed associated with abnormalities in LV function (see section 4.0 below). However, as will be highlighted in subsequent discussion, whether

these effects can be explained by obesity-induced LVH is controversial. This controversy is in-part what prompted me to further explore the role of obesity-induced LVH as an important determinant of the transition to LV dysfunction.

3.1 Obesity and left ventricular geometry: Eccentric, concentric or both?

As highlighted in section 2.4.4 above, when considering the role of obesity-induced LVH as a possible cause of LV dysfunction (see section 4.0 below), it is also important to consider the LV remodelling process that coexists with LVH. As previously indicated, it is more likely that eccentric LVH will progress to LV systolic chamber dysfunction, whilst concentric LVH is more likely (but not exclusively) to progress to LV diastolic dysfunction. With respect to obesity, the prevailing hypothesis is that the load that the LV faces is driven largely by increases in blood volume which result in an enhanced cardiac output and stroke volume (Stoddard et al 1992, Messerli et al 1983). The chronic volume overload results in an increase in LV filling volumes and thus an augmented preload and myocardial oxygen demand. The compensatory change that occurs is thus cardiomyocyte growth which is intended to reduce wall stress and myocardial oxygen demand by increasing the wall thickness of the heart. If wall thickness does not increase in keeping with increments in filling volumes, LV wall stress may increase (Alpert et al 1995, Berkalp et al 1995, Zarich et al 1991), the consequence potentially being a failed myocardium. Although there is no doubt that severe obesity is associated with a cardiomyopathy attributed to chronic volume overload which is characterized by LV dilatation (Alpert et al 2001), there is nevertheless dispute as to whether the primary remodelling process in obesity is concentric (which is likely to progress mainly to diastolic heart failure) or eccentric (which is likely to progress in the first instance to systolic heart failure). What is the evidence for or against a concentric or eccentric LV remodelling process in obesity?

Earlier studies suggested that the predominant effect of obesity on LV structure is eccentric LVH (LV end diastolic diameter increases in proportion to wall thickness with no

change in relative wall thickness) (Messerli et al 1983, Messerli et al 1982, Lauer et al 1992, Gottdiener et al 1994, de Simone[a] et al 1994). This notion has been supported by some larger studies also showing a lack of impact of body size on relative wall thickness despite an increase in LVM (Kizer et al 2004, Fox et al 2004). However, alternative studies indicate that adiposity may be associated with a relatively greater increase in LV wall thickness as compared to LV end diastolic diameter with an increased relative wall thickness (concentric LV remodelling and concentric LVH) being the primary consequence (Mensah et al 1999, Gutin et al 1998, Avelar et al 2007, Peterson et al 2004, Wong et al 2004, Woodiwiss et al 2008). The uncertainty as to whether overweight or obesity promotes primarily eccentric or concentric LVH in these studies may be attributed to a number of problems.

Inconsistencies in studies reporting on the LV geometric remodelling process associated with obesity may be attributed to the use of small study samples (Messerli et al 1983, Messerli et al 1982, 1983, Mensah et al 1999, Gutin et al 1998, Peterson et al 2004, Wong et al 2004), non-random recruitment approaches (Messerli et al 1983, Messerli et al 1982, 1983, Gottdiener et al 1994, de Simone[a] et al 1994), the assessment of study groups with a limited BP range (Lauer et al 1991, Lauer et al 1992), the use of a high proportion of previously treated participants (~44-90% of participants) (Gottdiener et al 1994, Kizer et al 1994, Fox et al 2004), the assessment of adiposity indices employed as discrete traits (Messerli et al 1983, Messerli et al 1982, Lauer et al 1991, Lauer et al 1992, Gottdiener et al 1994, de Simone[a] et al 1994, Fox et al 2004, Avelar et al 2007, Peterson et al 2004, Wong et al 2004), and the recruitment of patients with severe obesity (BMI>35 kg/m^2) only (Avelar et al 2007). Further, in some studies showing relations between excess adiposity and relative wall thickness, adjustments were not made for confounders (Mensah et al 1999, Gutin et al 1998, Peterson et al 2004). Thus, there are many reasons to explain the uncertainty that exists regarding the impact of obesity on LV geometry.

More recent evidence obtained by our group which addressed all of the aforementioned concerns indicates that obesity is indeed associated with concentric LV remodelling and hypertrophy (Woodiwiss et al 2008). However, in a subsequent study

conducted in a large, randomly selected population sample with a high prevalence of obesity (The Strong Heart Study) the authors reported that obesity was associated with a decrease in relative wall thickness (eccentric LV remodelling) despite an increased LVMI (De Simone et al 2011). Moreover, in a recent large community-based study although obesity was associated an increased LVMI, no increases in relative wall thickness were noted (Russo et al 2011). Of note is that in all of the prior studies, echocardiographic techniques wrere employed to assess LV dimensions. In contrast, in the The Multi-Ethnic Study of Atherosclerosis (MESA), where much more accurate magnetic resonance imaging assessments of LV dimensions and mass were evaluated in 5098 participants, although obesity was associated with increasing LV volumes, the extent of LVH exceeded the increase in LV volumes, and thus obesity was associated with concentric LVH (Turkbey et al 2010). In summary, obesity can be considered to be related to concentric LV remodelling, but the nature of the concentric remodelling is atypical in that chamber volumes may also be increased. Therefore, based on the geometric LV remodelling process noted in obesity, it is possible that obesity-induced LVH may progress to either diastolic or systolic dysfunction. What is the evidence that obesity is associated with LV dysfunction and is there sufficient evidence to suggest that this may be attributed to LVH or the LV geometric remodelling process?

4.0 Excess adiposity and cardiac dysfunction

In the Multiethnic Study of Atherosclerosis, the independent relationship between obesity and congestive heart failure was reduced from an 83% to a 58% risk of heart failure with the inclusion of left ventricular EF in the regression model (Bahrami et al 2008). These data indicate that decreases in LV systolic chamber function, which in otherwise well individuals is a well established risk factor for the development of heart failure (Bahrami et al 2008), is a potentially important mechanism through which obesity promotes heart failure. However, not all studies support the view that the relationship between excess adiposity and

heart failure can be explained by the development of cardiac dysfunction. Indeed, the risk of heart failure that is explained by waist-to-hip ratio may persist even with adjustments for measures of cardiac function, including EF and measures of diastolic dysfunction (Spies et al 2009). Is there additional evidence to support a view that excess adiposity may mediate heart failure through direct effects on the heart?

4.1 Excess adiposity may cause cardiac dysfunction through direct effects on the heart.

A number of pre-clinical studies have provided evidence to suggest that cardiomyocyte dysfunction or damage to the heart may occur in obese states (Caroll et al 2006, Relling et al 2006, Dong et al 2006, Ren et al 2000, Barouch et al. 2006, Zhou et al 2000). However, as many of the animal models employed in these studies (Caroll et al 1997, Relling et al 2006, Dong et al 2006, Ren et al 2000, Barouch et al. 2006, Zhou et al 2000, Majane et al 2009) also have associated conventional cardiovascular risk factors, whether the outcomes of these studies are indeed beyond all conventional risk factors is uncertain. Is there evidence from human studies to suggest that obesity may cause abnormalities in diastolic or systolic chamber function? In the following sections I will review the evidence to support or refute a role for obesity as a cause of diastolic or systolic cardiac function independent of traditional risk factors. I will underscore the evidence or lack thereof to suggest that these processes may be driven by preceding LVH or an abnormal LV remodelling. I will also highlight the deficiencies in these data and develop the arguments to support the hypotheses generated and tested in the current thesis.

4.1.1 Excess adiposity as a cause of abnormalities in diastolic function of the left ventricular chamber.

In the more recent past, several cross-sectional studies conducted in small (Peterson et al 2004, Wong et al 2004) and large (Redfield et al 2003, Ammar et al 2008, Fischer et al

2003, Tsioufis et al 2009, Powell et al 2006, Russo et al 2011) study groups and in both select study populations (Tsioufis et al 2009, Peterson et al 2004, Wong et al 2004) and randomly selected community samples (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003, Powell et al 2006, Russo et al 2011) have suggested that independent of alternative risk factors, even modest levels of obesity contribute toward the pathogenesis of an abnormal LV diastolic function. Moreover, some studies suggest that weight loss induced either by gastric bypass surgery (Willens et al 2005, Leichman et al 2008, Rider et al 2009, Hsuan et al 2010, Owan et al 2011) or by lifestyle intervention (Wong et al 2006) results in improvements in myocardial diastolic function independent of conventional cardiovascular risk factors. With the exception of one relatively large study (n=423) conducted in severely obese patients (Owan et al 2011), these intervention studies were conducted in small study samples and hence may reflect the effects of a selection bias or false positive findings. In contrast to studies reporting on relationships between excess adiposity and abnormalities in LV diastolic function, some cross-sectional studies conducted in a large study sample have failed to establish a contribution of obesity toward the pathogenesis of an abnormal LV diastolic function (Bella et al 2002, Chinali et al 2006, De Simone et al 2011) and others have demonstrated a relatively minor contribution of obesity to LV diastolic function (Fischer et al 2003). Moreover, some studies suggest that weight loss is not associated with improvements in LV diastolic dysfunction (Leichman[a] et al 2006, Skilton et al 2007). There are several potential explanations for differences in results between studies.

Differences in the anthropometric measures employed to index obesity, where measures of central adiposity may be more closely associated with abnormalities of LV diastolic chamber function than BMI (Ammar et al 2008, Tsioufis et al 2009), could explain discrepancies between studies. In this regard, in the cross-sectional studies where relationships between obesity and LV diastolic function were not clearly demonstrated, only the effects of BMI were evaluated (Bella et al 2002, Chinali et al 2006, De Simone et al 2011). In this regard, as will be discussed in section 5.0, indices of abdominal adiposity are more likely to be associated with the metabolic disturbances that accompany obesity and

these disturbances could explain many of the myocardial changes that contribute toward LV dysfunction. Whether relationships between BMI and LV diastolic dysfunction are easily detected in populations where metabolic disturbances that accompany obesity are closely associated with the extent of abdominal obesity, is uncertain.

A second potential explanation for the variable relationships between obesity and LV diastolic function is the extent to which obesity is associated with concentric LVH or concentric LV remodelling in some but not other populations. As indicated in section 2.2 4 in the aforementioned discussion, LV diastolic dysfunction is strongly determined by LVM or concentric LV remodelling (Schillaci et al 2002, Fischer et al 2003, Chahal et al 2010), whilst the relatiopnship between excess adiposity and concentric LV remodelling is highly variable. Indeed, in the Strong Heart Study, which has consistently revealed a lack of relationship between BMI and E/A (Bella et al 2002, Chinali et al 2006, De Simone et al 2011), obesity was associated with a decrease in relative wall thickness (eccentric LV remodelling) (De Simone et al 2011). In contrast, after adjustments for LVM, the previously described relationships between obesity and LV diastolic function were considerably reduced, suggesting an important role for LVH (possibly concentric LVH) in mediating the obesity-induced decreases in diastolic function (Fischer et al 2003). However, whether the impact of obesity on diastolic function is determined by the LV remodelling process may not be an appropriate explanation as in one study demonstrating a strong independent relationship between increasing categories of BMI and a decreased E/A, relative wall thickness was unrelated to BMI (Russo et al 2011). Nevertheless, in none of the aforementioned studies demonstrating relationships between obesity and E/A (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003, Tsioufis et al 2009, Powell et al 2006, Russo et al 2011) was the impact of adjustments for LV relative wall thickness evaluated. Thus, further studies are required to assess this question.

A third potential explanation for discrepancies between studies demonstrating inconsistencies in relationships between obesity and LV diastolic function is that in some, but not other populations, the impact of alternative haemodynamic factors such as 24-hour BP

or arterial stiffness, may be more pronounced than in other populations. In this regard, 24-hour BP is a better measure of long-term BP loads on the heart and hence a better measure of obesity-induced target organ changes. Moreover, arterial stiffness is a key determinant of aortic BP, and brachial BP may not closely reflect aortic BP values. Indeed, aortic pulse wave velocity (PWV), the current "gold-standard" (referrant) method of assessing arterial stiffness, is also well recognised as an independent predictor of target organ changes. Whether or not obesity mediates adverse effects on LV diastolic function through 24-hour BP or arterial stiffness has important therapeutic implications. Thus, further studies are required to address these questions.

Because a number of questions arise from our current understanding of the role of obesity in mediating LV diastolic function, as part of the present thesis I therefore assessed the extent to which an excess abdominal as opposed to general adiposity contributes toward LV diastolic function in a community sample with a high prevalence of obesity; whether LVH or LV relative wall thickness play an important role in mediating the impact of obesity on LV diastolic function; and whether 24-hour BP or aortic stiffness contribute toward the impact of obesity on abnormalities of LV diastolic function. These data are described in chapters 2 and 3 of the present thesis and have been published in-part in the *Am J Cardiol* (Libhaber et al 2009).

4.1.2 Excess adiposity as a cause of abnormalities in systolic function of the left ventricular chamber.

Load-independent tissue Doppler indices of systolic myocardial function have been shown to be reduced in overweight and obese people without conventional cardiovascular risk factors (Peterson et al 2004, Wong et al 2004). However, the independent relationship between excess adiposity and LV systolic chamber function is controversial, with some studies showing a relationship between excess adiposity and systolic function (Ammar et al 2008, Chinali et al 2006, Scaglione et al 1992, Karason et al 1998, Alpert et al 1995), whilst

other earlier studies have failed to do so (Pascual et al 2003, de Devitiis et al 1981, Zarich et al 1991, Stoddard et al 1992, De Simone[b] et al 1996, Mureddu et al 1996, Iacobellis et al 2002, Peterson et al 2004, Wong et al 2004). Moreover, more recent studies conducted in large samples have provided strong evidence that obesity is not associated with a reduced LV systolic chamber function (Turkbey et al 2010, Powell et al 2006, Bazzano et al 2011, Russo et al 2011). Furthermore, even with the use of load-independent tissue Doppler measures of myocardial as opposed to chamber function, or with chamber function assessments, weight loss produced by either lifestyle modification or gastric bypass does not influence left ventricular systolic function (Willens et al 2005, Rider et al 2009, Wong et al 2006, Skilton et al 2007). Nevertheless after gastric bypass surgery in 423 patients with severe obesity, LV midwall fractional shortening, an index of myocardial systolic function, increased (Owan et al 2011). Although there is more evidence against rather than in favour of obesity producing decreases in LV systolic chamber function, it should be clearly evident that there is still considerable controversy as to whether obesity contributes toward decreases in LV systolic chamber or even regional myocardial function. What are the possible explanations for the discrepant outcomes of studies assessing the role of obesity as a potential determinant of LV systolic dysfunction?

As it is more likely that eccentric LV remodelling will progress to LV systolic chamber dysfunction (see section 2.2.4 above), it is possible that one potential explanation for the variable results of studies assessing the relationship between obesity and LV systolic chamber function is that obesity may have different effects on the LV remodelling process (see discussion in section 3.1). This is nevertheless an unlikely explanation as a number of studies performed in large study samples have demonstrated that although obesity is a principle risk factor for increased chamber dimensions, that this does not translate into a reduced LV systolic chamber function (Bazzano et al 2011, Russo et al 2011, Turkbey et al 2010). What alternative possibilities may explain the variable relationship between obesity and LV systolic chamber dysfunction?

As discussed in section 2.2.3, if LVH is to translate into a reduced LV systolic chamber function, it is important that the hypertrophic process exceeds that predicted from workload (inappropriate LVM). That is, a factor other than the workload to which the LV is exposed, should be driving this process. The same principle would hold for obesity-induced LVH. That is, if obesity can produce LVH in excess of that to which the LV is exposed, then this may result in a reduced LV systolic chamber function. Thus, it would only be in circumstances where obesity is responsible for a high proportion of individuals having inappropriate LVM that obesity may ultimately cause LV systolic dysfunction. Can obesity produce inappropriate LVH? In this regard there are indeed reports to suggest that obesity may be an important determinant of the development of inappropriate LVH (see subsequent paragraph). Thus, obesity may promote the transition from compensated LVH (LVH within a range of values predicted from workload) to LV systolic chamber dysfunction once it induces inappropriate LVH. In support of this hypothesis is work produced by our group to show that premature LV pump dysfunction and cardiomyocyte apoptosis may occur in spontaneously hypertensive rats (SHR) following the addition of an obesity-inducing diet, and that this was associated with a marked exacerbation of LVH in the SHR (Majane et al 2009). Under these circumstances, it is likely that variable results will be obtained when assessing relations between excess adiposity and LV systolic chamber function depending on the extent to which obesity has produced inappropriate LVM.

Although the hypothesis that obesity may promote the transition from compensated LVH to LV systolic chamber dysfunction only once it induces inappropriate LVH, is indeed an attractive hypothesis, there are a number of outstanding issues with respect to this hypothesis. First, the extent to which excess adiposity contributes toward the variability in inappropriate LVM at a community level is uncertain. Although there are a number of studies that have demonstrated a higher BMI in participants with as compared to those without inappropriate LVH, there are similarly an equal number of studies that have failed to show this relationship. What is the evidence to support or refute the notion that obesity is a major determinant of an increased LVM exceeding that predicted from stroke work?

With respect to studies demonstrating an increased BMI in those with inappropriate LVH, in 28 hypertensive participants of the LIFE study with inappropriate LVM, but without LVH, BMI was increased as compared to 180 participants without inappropriate LVM or LVH (Palmieri et al 2004). As compared to 67 hypertensives without inappropriate LVH, in 51 hypertensives with inappropriate LVH, BMI was increased (Lopez et al 2007). In addition, in 659 participants of the LIFE study, as compared to 354 participants without, 305 participants with inappropriate LVH had an increased BMI (Palmieri et al 2001). Moreover, as compared to 1284 hypertensives of the Hypertension Genetic Epidemiology Network (HyperGen) study without inappropriate LVH, 229 hypertensives with an inappropriate LVH had an increased BMI (de Simone et al 2004). As compared to 275 hypertensives without, 84 hypertensives with inappropriate LVH had a modest increase in BMI (27.4±4.4 vs 28.6±4.3 kg/m^2, p=0.032)(Chinali et al 2007). As compared to 114 and 113 normal weight and overweight adolescents respectively, 223 obese adolescents had an increased LVM_{inappr} (Chinali et al 2006). As compared to 164 hypertensives without, 16 hypertensives with inappropriate LVH had a higher BMI (Palmieri et al 1999). As compared to 185 normotensives without, 25 normotensives with inappropriate LVH had a higher BMI, but in 231 hypertensives without, 64 hypertensives with inappropriate LVH had no differences in BMI (Celentano et al 2001). Last, as compared to 259 hypertensives without, 143 hypertensives with inappropriate LVH had a higher BMI (Ratto et al 2008).

In contrast to the aforementioned studies demonstrating relations between excess adiposity and inappropriate LVH, a number of studies have also failed to demonstrate these relationships. In 294 hypertensives consecutively assessed at a University Hospital centre, BMI was equivalent in those with as compared to those without inappropriate LVH (de Simone et al 2001). Furthermore, in 104 of 522 hypertensives who showed regression of inappropriate LVH with antihypertensive therapy, BMI increased over the treatment period (Muiesan et al 2007). In 562 subjects (231 normotensives obtained from Hospital staff and other sources and the remaining hypertensives referred to a Hospital clinic), BMI was similar between participants with, as compared to those without an inappropriate LVH (Mureddu et

al 2001). Also in 340 high risk participants, BMI was almost identical in those with as compared to without inappropriate LVH (Cioffi et al 2011). In summary, there is considerable uncertainty as to the role of obesity as a determinant of LVM_{inappr}. Previous studies have been conducted in either select clinical samples or in adolescents. Hence, whether the results reflect a selection bias or effects that occur early in life is uncertain. Moreover, in none of these studies were relationships between BMI or alternative adiposity indices assessed in continuous analysis with adjustments for confounders. Furthermore, discrepancies between studies demonstrating inconsistencies in relationships between obesity and LVM_{inappr} is that in some, but not other populations, the impact of alternative haemodynamic factors such as 24-hour BP or arterial stiffness, may be more pronounced than in other populations. In this regard, as indicated in the aforementioned discussion, 24-hour BP is a better measure of long-term BP loads on the heart and hence a better measure of obesity-induced target organ changes. Indeed, in one study both BMI and 24-hour BP were increased in 16 hypertensives with inappropriate LVH as compared to 164 hypertensives with an appropriate LVM (Palmieri et al 1999). Moreover, arterial stiffness is a key determinant of aortic BP, and brachial BP may not closely reflect aortic BP values. Indeed, aortic PW, is also well recognised as being an independent predictor of target organ changes. Whether or not obesity mediates adverse effects on LVM_{inappr} through 24-hour BP or arterial stiffness has important therapeutic implications. Thus, further studies are required to address these concerns. Hence, as described in chapter 4, as part of the present thesis I examined the extent to which excess adiposity contributes toward the variability of LVM_{inappr} independent of a number of haemodynamic factors in a community sample with a high prevalence of obesity.

As highlighted in section 2.2.3 above, there are also a number of outstanding issues which require clarity with respect to the hypothesis that it is LVM_{inappr} rather than LVM or LVMI that contributes toward a reduced LV systolic chamber dysfunction. The controversy related to these questions has been discussed in section 2.2.3. Thus in chapters 4 and 5 of the present thesis I have also provided evidence to further substantiate the hypothesis that

inappropriate LVH may account for the transition to LV systolic chamber decompensation. These data have been published in-part in the journals *Hypertension* and *J Hypertens* (Libhaber et al 2013, Woodiwiss and Libhaber et al 2012).

5.0 Insulin resistance as a potential mechanism responsible for obesity-associated left ventricular hypertrophy or dysfunction.

From a therapeutic perspective, it is important to understand the mechanisms that may explain the transition from obesity-induced LVH to LV dysfunction. As indicated in the aforementioned discussion, it is possible that LV dysfunction in obesity may be attributed to the adverse effects of concentric or eccentric LVH on either LV diastolic or systolic chamber function. Alternatively, obesity may promote LV diastolic or systolic chamber dysfunction independent of effects on LVH or LV geometry. It is therefore important to consider possible mechanisms that may explain obesity-induced increases in either LVM or LV dysfunction.

In the present section I will review the evidence to suggest a potential role for insulin resistance in mediating obesity-induced increases in LVM or the transition to LV dysfunction. In this regard, a number of alternative mechanisms have been suggested, but this was the only potential mechanism that I explored in the present thesis. Thus, a review of alternative mechanisms goes beyond the scope of the present thesis. In the present section I will first discuss the concept of obesity-induced insulin resistance. Secondly, I will suggest possible changes that occur in insulin resistance that may explain the adverse effects of insulin resistance on the heart. Last, I will summarise the evidence to indicate that obesity-induced effects on LVM and LV dysfunction in human studies may be explained by insulin resistance and describe the studies performed in the present thesis in the context of evidence still required to either support or refute these hypothesis.

5.1 Insulin resistance in obesity

Insulin resistance may occur as a consequence of excess adiposity and this effect is more closely associated with the extent of abdominal as opposed to general obesity (Kahn and Flier 2000). At a cellular level, insulin binds to its receptor on the surface of target cells, thereby causing tyrosine autophosphorylation and consequent intracellular signaling. These events culminate in cellular responses, such as the translocation of glucose transporters to the cell surface to allow glucose uptake for use or glycogen storage. In obesity, however, insulin signaling may be defective. Insulin-stimulated protein kinase activity of the insulin receptor, which mediates tyrosine autophosphorylation, is reduced in obese as compared to non-obese people, and it is further reduced in patients with obesity-induced type II diabetes mellitus (Caro et al 1989). However, euglycaemia is maintained in the initial stages of insulin-resistance through compensatory hyperinsulinaemia. Indeed, there is considerable evidence to suggest that a large proportion of obese individuals are insulin-resistant, but that compensatory hyperinsulinaemia maintains fasting blood glucose concentrations (Reaven 2003). Thus, insulin resistance goes undetected in these individuals.

5.2 Adverse effects of insulin resistance that may influence the myocardium.

Insulin resistance will undoubtedly promote adverse cardiovascular effects once type II diabetes mellitus develops and the effects of hyperglycaemia are noted. However, insulin resistance may also induce adverse cardiac changes prior to the development of diabetes mellitus and poor blood glucose control through a number of mechanisms. In this regard, insulin resistance is not specific to skeletal muscle, but also involves myocardial muscle tissue as well (Nikolaidis et al 2004, Ouwens et al 2005, Coort et al 2007) where it downregulates glucose uptake and hence precludes the energetic advantage provided by glucose versus free fatty acid oxidation (Nikolaidis et al 2004, Ouwens et al 2005). Moreover, insulin resistance is associated with an accumulation of intracellular triacylglycerol which promotes lipotoxicity (Coort et al 2007). In addition, hyperinsulinaemia, that occurs as a consequence of insulin resistance, promotes obesity-induced increases in sympathetic

nervous system activity (Esler et al 2001). Importantly, LVH is associated with excessive myocardial sympathetic effects (Schlaich et al 2003) and activation of the sympathetic nervous system can promote the transition from compensated LVH to LV systolic dysfunction through mechanisms that appear to be unrelated to BP changes (Badenhorst et al 2003, Veliotes et al 2005). Furthermore, insulin may directly promote cardiomyocyte growth through a number of mechanisms (Samuelsson et al 2006).

Insulin resistance is often associated with leptin resistance and a reduced cardiac efficiency and an altered myocardial substrate metabolism may accompany obesity associated with leptin deficiency or leptin resistance (Buchanan et al 2005). These changes in myocardial substrate metabolism may contribute toward an increased cardiomyocyte apoptosis in obesity models of leptin deficiency or leptin resistance (Barouch et al 2006). The cardiomyocyte apoptosis in leptin resistant or leptin deficient animals is thought to occur through a reduced cardioprotection mediated by leptin, possibly induced via a resultant increase in ectopic lipid overload in cardiac myocytes (lipoapoptosis) (Zhou et al 2000). Irrespective of the potential adverse myocardial changes that may be mediated by insulin resistance, an important question is to what extent does the current evidence suggest that obesity in humans may promote LVH or LV dysfunction through the presence of insulin resistance?

5.3 Insulin resistance as a possible cause of left ventricular hypertrophy

Data showing independent relationships between insulin resistance and LVM are conflicting. In this regard, there are a number of studies that have shown such relationships, but similarly, there are also a number that have failed to demonstrate marked independent relationships. In this section I will first describe the studies that have demonstrated important relationships and subsequent to this, I will summarise those that have been unable to show similar independent relationships.

A number of studies with small sample sizes conducted in select patient populations have provided evidence to support a role for insulin resistance as a possible mechanism involved in LVMI. In a small study sample of hypertensives, but not in normotensives, fasting plasma insulin concentrations were associated with LVM independent of BP and BMI (Sharp et al 1992). In 40 normotensive, non-diabetic obese participants, insulin resistance (intravenous glucose tolerance test) and the associated hyperinsulinaemia were strongly associated with LVM independent of BMI and BP (Sasson et al 1993). In 50 hypertensives insulin sensitivity was associated with LV wall thickness independent of BMI (Lind et al 1995). In 40 non-diabetic, hypertensives, an association between insulin sensitivity, determined with a modified euglycaemic insulin clamp technique, and LVMI was demonstrated (Kamide et al 1996). In 25 hypertensives with LVH, as compared to 12 hypertensives without LVH matched for BMI, a greater degree of insulin resistance, as determined using the euglycaemic insulin clamp technique was noted (Paolisso et al 1995). In 26 hypertensives, insulin resistance, as assessed from the euglycaemic insulin clamp technique was associated with LV wall thickness independent of BMI and BP (Paolisso et al 1997). In 52 hypertensives, urinary excretion rates of C-peptide were associated with LVM (Tomiyama et al 1997). In 29 obese, but not lean participants, the area under the curve for circulating insulin concentrations after oral glucose loading was associated with LVM (Vetta et al 1998). Furthermore, in 29 non-obese, non-diabetic, glucose tolerant participants with a high-normal BP, insulin sensitivity (minimal model of glucose kinetics) was related to LVM independent of BP (Phillips et al 1998). In 26 hypertensives with impaired gluocse tolerance, 39 hypertensives with a normal glucose tolerance and in 18 normotensives, insulin resistance, as determined from the insulin suppression test was independently associated with LVMI and change in insulin resistance was associated with change in LVMI during angiotensin-converting enzyme inhibitor treatment (Watanabe et al 1999). In 49 male but not in 42 female hypertensives, the homeostasis model assessment of insulin resistance (HOMA-IR), which mirrors the outcomes of the more sensitive glucose clamp technique (Bonara et al 2000), was associated with LVM independent of BMI (Shigematsu et al 2006).

In 41 patients with untreated essential hypertension and LVH, HOMA-IR was noted to be independently associated with LVH (Anan et al 2007). In 230 hypertensives, HOMA-IR was associated with LVH independently of BMI or waist circumference (Sesti et al 2007). However, in this study neither BMI nor waist circumference were related to the presence of LVH (Sesti et al 2007).

The relatively small sample sizes (n=29-230) and the use of select clinical populations in the aforementioned studies obviously raises the question of false positive associations and a selection bias. Nevertheless, glucose intolerance without diabetes mellitus was associated with LVM indexed to height$^{2.7}$ in 1345 non-diabetic patients (457 of whom had glucose intolerance) (Ilercil et al 2001). In that study (Ilercil et al 2001) glucose intolerance in non-diabetic participants was presumably attributed to insulin resistance, but this relationship was not assessed. Furthermore, in a community sample of 820 70 year olds, HOMA-IR was strongly associated with LVMI and relative wall thickness, but these relations were not adjusted for indices of adiposity (Sundstrom et al 2008). Moreover, in 767 never-treated hypertensives, an index of insulin resistance (Matsuda index/ISI) or fasting circulating insulin concentrations were associated with LVM indexed to body surface area independent of waist circumference and BMI and additional confounders (Sciacqua et al 2011). However, the inclusion of two indices of obesity (waist circumference and BMI) in the same multivariate model in this study (Sciacqua et al 2011) is likely to diminish the effect of an adjustment for either parameter. Last, in 1599 participants being evaluated for health checks, HOMA-IR was associated with LVM, but this relationship was not adjusted for indices of excess adiposity (Hwang et al 2011).

Evidence suggesting that insulin resistance without diabetes mellitus is either not associated with or is only modestly associated with either LVM or geometry independent of confounding factors also comes from studies with both small and large sample sizes conducted in select and unselected samples. In 33 hypertensives, parameters of insulin metabolism were not associated with LVMI (Nagano et al 1994). In 93 unselected participants, fasting plasma insulin concentrations were not associated with LVM

independent of body weight or systolic BP (Kupari et al 1994). In 29 hypertensives, fasting plasma insulin was not correlated with LVM (Costa et al 1995). Furthermore, although in 180 male hypertensives and 210 normotensives, insulin sensitivity was associated with LV relative wall thickness independent of BMI, no independent relationship was noted with LVMI (Ohya et al 1996). In 24 obese participants, the intravenous glucose tolerance test was not independently associated with LVM (Avignon et al 1997). Moreover, in 27 overweight/obese and 31 age-matched controls, no relationship between HOMA-IR and LVM was noted (Merudda et al 1998). In 30 hypertensives, fasting plasma insulin concentrations were not associated with LVM (Jelenc et al 1998). In addition, in 101 never-treated, non-diabetic, hypertensive subjects, insulin and insulin growth factor-1 were, but HOMA-IR was not associated with LVM and geometry independent of BMI (Verdecchia et al 1999). Moreover, post-load glucose and insulin concentrations, measured two hours after glucose administration, were noted to be more important than fasting insulin as a potential determinant of LVM (Verdecchia et al 1999). In 50 subjects without diabetes mellitus, insulin concentration, secretion or action (euglycaemic clamp) was not independently associated with LVM when accounting for body mass or blood pressure (Galvan et al 2000). In 51 hypertensives, neither insulin resistance as assessed using the euglycaemic insulin clamp, nor circulating insulin concentrations were related to LVM indexed to height independent of BMI (Malmquist et al 2001). In 89 hypertensives, no relationship between insulin resistance, as assessed using the euglycaemic insulin clamp technique, and LVM or remodeling was noted (Olsen et al 2003). Moreover, in 153 healthy subjects, neither insulin resistance (HOMA-IR), nor fasting insulin concentrations were associated with LVH, independent of obesity (Ebnic et al 2006).

In the aforementioned studies showing a lack of relationship between insulin or insulin resistance and LVM, the small study sizes and the use of select patient populations may have resulted in false negative results or a selection bias. However, C-peptide concentrations were not associated with LVM independent of BMI and BP in 1315 participants from a population survey (Chen et al 1998). Furthermore, In 470 elderly men,

insulin resistance assessed from the euglycaemic insulin clamp technique was associated with relative wall thickness, but not with LVMI (Sundstrom et al 2000). However, in that study (Sundstrom et al 2000) the relationship between insulin resistance and relative wall thickness was not adjusted for BMI. Moreover, in 1542 hypertensives without diabetes mellitus of the Hypertension and Genetic Epidemiology (HyperGen) study, independent of BMI, no relationship between circulating insulin concentrations and LVM were noted (Devereux et al 2002). However, in that study (Devereux et al 2002) there was a weak independent relationship with relative wall thickness. Furthermore, in a large community-based sample of 2623 Framingham Study subjects, although LVM and wall thickness increased with worsening glucose intolerance and insulin resistance (as determined by HOMA-IR) in non-diabetic participants, an effect that was more striking in women compared with men, this relation was eliminated when adjusting for body size (Rutter et al 2003). Furthermore, in 1603 Framingham Study subjects although magnetic resonance imaging-determined LVM indexed to height increased across quartiles of HOMA-IR, this relationship was abolished with adjustments for BMI (Velagaletti et al 2010). Moreover, in 2399 African Americans of the Jackson Heart Study, although trends for associations between insulin resistance and indices of LV remodelling were noted independent of BMI in categories of fasting blood glucose concentrations, no relationships between HOMA-IR and LVM index were noted after adjustments for BMI (Fox et al 2011). Last, in the Strong Heart Study, a large (1068 men and 1851 women) population-based study conducted in an American-Indian population with a high prevalence of excess adiposity, HOMA-IR was not independently associated with LVM or LV geometry (de Simone et al 2003, 2011).

Despite the conflicting evidence for an independent relationship between insulin resistance and LVM, apart from one small study conducted in 53 hypertensives with electrocardiographic LVH from the LIFE study showing no irelationship between circulating insulin concentrations and LVM_{inappr} (Olsen et al 2004), no studies have been performed to assess the relationship between insulin resistance and the presence of inappropriate LVM. Hence, it is uncertain whether relationships between insulin resistance and LVM beyond that

predicted from LV workload are independent of indices of excess adiposity. As in the present thesis I was able to show that obesity was the main factor independently associated with inappropriate LVM, and that inappropriate LVM and regression of inappropriate LVM were strongly related to EF, I evaluated whether insulin resistance could account for the effect of obesity on inappropriate LVM. These data and the implications thereof are described in chapter 6 of the present thesis.

5.4 Insulin resistance as a possible cause of abnormalities of left ventricular function

As with the conflicting data reporting on relationships between insulin resistance and LVM beyond body size, similar disparities exist with respect to the association of insulin resistance with LV dysfunction independent of adiposity indices. What is this evidence? In 33 hypertensives, although those with an impaired glucose tolerance had a reduced E/A, E/A was unrelated to the area under the insulin curve after an oral glucose load (Nagano et al 1994). In 50 hypertensives, insulin resistance, as assessed using the euglycaemic insulin clamp technique, was associated with E/A, whether this association survived adjustments for adiposity indices is uncertain (Lind et al 1995). In 27 otherwise healthy overweight and obese participants, 12 of whom had insulin resistance, insulin resistance was not associated with LV isovolumic relaxation time (an index of LV diastolic relaxation) after adjusting for body weight (Mureddu et al 1998). In 29 hypertensives men, insulin resistance, as assessed using the euglycaemic insulin clamp technique was associated with LV isovolumic relaxation time independent of BMI (Galderisi et al 1997). In 26 hypertensives with an impaired glucose tolerance, 39 hypertensives with a normal glucose tolerance and 18 normotensives, insulin resistance, as determined from the insulin suppression test, was related to E/A independent of BMI (Watanabe et al 1999). In 89 hypertensives, insulin resistance, as assessed with the euglycaemic insulin clamp technique was not independently associated with E/A and LV isovolumic relaxation time (Olsen et al 2003). In 109 obese and 33 normal weight participants, fasting insulin concentrations were inversely correlated with tissue Doppler

indices of both systolic and diastolic myocardial but not chamber function (Wong et al 2004). In 29 participants with a normal glucose tolerance, 20 with impaired glucose tolerance and 70 with type II diabetes mellitus, insulin resistance, as identified from the Quantitative Insulin Sensitivity Check Index was associated with LV diastolic dysfunction independent of BMI and waist-to-hip ratio (Bajraktari et al 2006). In 208 patients with normal ejection fraction of whom 57 had type 2 diabetes, insulin resistance was independently associated with left ventricular diastolic dysfunction in subjects without overt type 2 diabetes (Dinh W et al, 2010).

Although in 29 insulin resistant and 36 insulin sensitive women, diagnosed on the basis of HOMA-IR, LV peak filling rate, an index of an abnormal diastolic function was reduced, it is uncertain whether these differences were independent of adiposity indices (Utz et al 2011). Similarly, in 42 prediabetic adults with a HOMA-IR above 2.7, as compared to 79 prediabetics with a HOMA-IR below 2.7, although E/A was reduced (Sliem et al 2011), whether these differences were independent of adiposity indices is uncertain. Furthermore, in 92 participants either with or without an impaired glucose tolerance or diabetes mellitus, HOMA-IR was not correlated with E/A (Wada et al 2010) and in 102 otherwise healthy individuals although visceral fat was associated with diastolic dysfunction, HOMA-IR was not (Wu et al 2011). In 18 lean and 25 overweight/obese people, although tissue Doppler indices of diastolic function were noted to be abnormal in overweight or obese individuals, HOMA-IR did not account for these differences (Lambert et al 2010). The results of the aforementioned studies conducted in small sample sizes of select clinical populations, may nevertheless reflect inadequate sample sizes and a selection bias. What is the evidence with respect to studies conducted with a large sample size in unselected populations?

In 1603 Framingham participants, EF as assessed from magnetic resonance imaging was not associated with HOMA-IR (Velagaletti et al 2010). These data are consistent with the poor relationship between excess adiposity and LV systolic function as described in section 4.1.2. In 1542 hypertensives without diabetes mellitus of the HyperGen study, circulating insulin concentrations were not associated with EF or stress-corrected midwall

fractional shortening (a measure of myocardial systolic function) independent of confounders (Devereux et al 2002). In 2399 participants of the Jackson Heart Study, in women with a normal fasting blood glucose, HOMA-IR was related to a higher proportion with a lower EF after adjustments for BMI, but this only achieved marginal significance (p=0.02) (Fox et al 2011). In that study (Fox et al 2011), although diastolic function was assessed using transmitral velocity and tissue Doppler assessments, the results were not reported on. Lastly, in 1599 participants being evaluated for health checks, although increasing quartiles of HOMA-IR were associated with decreases in E/A and increases in E/e', whether these relationships survived adjustments for indices of excess adiposity was not reported on (Hwang et al 2011). Thus, in summary, the aforementioned studies were either characterised by small sample sizes in select clinical populations, thus raising the question of a selection bias confounding the results or type I or II statistical errors occurring, or positive relationships between HOMA-IR and diastolic function were not adjusted for indices of excess adiposity. Moreover, in some large studies relationship between indices of insulin resistance and LV diastolic function were noted, it is unclear whether the relationship was independent of adiposity indices. Hence, in the present thesis I evaluated whether HOMA-IR is associated with E/A in a relatively large, randomly selected community-based study sample independent of indices of excess adiposity. These data and the implications thereof are described in chapter 3 of the present thesis.

6.0 Summary of problem statements and aims of the thesis

As underscored in the aforementioned discussion, there are a number of areas of uncertainty with respect to the possible role of obesity in the transition from LVH to LV dysfunction. The following section summarises these areas of uncertainty (problem statements) and subsequently the study designs employed in the context of the aims of the present thesis. The chapters of the thesis, where each aim is addressed are also indicated.

6.1 Problem statements

With respect to the role of obesity in the transition from LVH to LV dysfunction:

1) The extent of the contribution of central as opposed to general obesity to abnormalities in LV diastolic function at a community level is uncertain.
2) The extent to which concentric LV remodelling accounts for obesity-induced abnormalities in LV diastolic function is uncertain.
3) Whether obesity is associated with abnormalities in LV diastolic function beyond all haemodynamic effects including 24-hour BP and large artery stiffness is unknown.
4) Whether obesity-associated relationships with abnormalities in LV diastolic function can be accounted for by insulin resistance is uncertain.
5) The extent to which obesity contributes toward the development of inappropriate LVH is unknown.
6) Whether obesity is associated with LVM_{inappr} beyond all haemodynamic effects including 24-hour BP and large artery stiffness is unknown.
7) Whether inappropriate LVH contributes toward a reduced EF independent of ablsoute LVM or LVMI is unknown.
8) Whether inverse relationships between inappropriate LVH and EF are accounted for by inappropriate LVH, residual confounding effects, or reverse causality is unknown.
9) Whether obesity associated relationships with inappropriate LVH are accounted for by insulin resistance is uncertain.

6,2 Aims

1) To address problem statements 1-3 above, I aimed to evaluate the extent of the contribution of central as opposed to general obesity to abnormalities in LV diastolic function at a community level; the extent to which concentric LV remodelling accounts for obesity-

induced abnormalities in LV diastolic function; and whether obesity is associated with abnormalities in LV diastolic function beyond all haemodynamic effects including 24-hour BP and large artery stiffness in a large cross-sectional, randomly selected, community-based sample with a high prevalence of obesity. This study is described in chapter 2 and has been published in-part in the *Am J Cardiol* (Libhaber et al 2009).

2) To address problem statement 4 above, I aimed to evaluate the relationship between HOMA-IR and LV diastolic function independent of indices of body size or obesity in a large cross-sectional, randomly selected, community-based sample with a high prevalence of obesity. This study is described in chapter 3.

3) To address problem statements 5-7 above, I aimed to evaluate the extent to which obesity contributes toward the development of inappropriate LVH independent of a number of haemodynamic factors and whether LVM_{inappr} is inversely associated with a reduced EF independent of absolute LVM or LVMI in a large cross-sectional, randomly selected, community-based sample with a high prevalence of obesity. This study is described in chapter 4 and is to be published in-part in *J Hypertens* (Libhaber et al 2012, in-press).

4) To address problem statement 8 above, I aimed to evaluate whether regression of LVM_{inappr} with antihypertensive therapy is associated with increases in on-treatment EF independent of changes in LVM or LVMI in a large single-centre clinical trial. This study is described in chapter 5 and has been published in *Hypertension* (Woodiwiss and Libhaber et al 2012).

5) To address problem statement 9 above, I aimed to evaluate the relationship between HOMA-IR and LVM_{inappr} independent of indices of body size or obesity in a large cross-sectional, randomly selected, community-based sample with a high prevalence of obesity. This study is described in chapter 6.

CHAPTER 2

Contribution of Central and General Adiposity to an Abnormal Left Ventricular Diastolic Function in a Community Sample with a High Prevalence of Obesity.

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

Abstract

The relative independent contribution of excess adiposity as indexed by measures of central, general or peripheral adiposity toward an abnormal cardiac diastolic chamber function at a community level is unclear. In 626 randomly selected participants over 16 years of age from a community sample with a high prevalence of excess adiposity (~24% overweight and ~43% obese) I assessed the independent contribution of indices of adiposity to the variation in E/A and to E/e'. After adjustments for a number of confounders including age, gender, pulse rate, conventional diastolic (or systolic) blood pressure (BP), antihypertensive treatment, left ventricular mass index (LVMI) and the presence of diabetes mellitus or an HbA1c>6.1%; waist circumference (p=0.0012) and body mass index (BMI) (p=0.02) were independently associated with a reduced E/A. In contrast neither waist-to-hip ratio (p=0.23) nor skin-fold thickness (p=0.37) were independently associated with E/A, and waist circumference was independently associated with E/A even after adjustments for other adiposity indices including BMI (p<0.05-0.005). No independent relationships between adiposity indices and E/e' were noted (n=212). In contrast to the effects on diastolic function, waist circumference was not correlated with left ventricular ejection fraction (p=0.83). The independent relationship between waist circumference and E/A (standardized β-coefficient=-0.11±0.04, p=0.0036) was second only to age (standardized β-coefficient=-0.54±0.04, p<0.0001) and similar to BP (standardized β-coefficient=-0.14±0.03, p<0.0001) in the magnitude of the independent effect on E/A. The inclusion of relative wall thickness rather than LVMI in the regression equation produced similar outcomes. The exclusion of LVMI and relative wall thickness from the regression equations, or the inclusion of carotid-femoral pulse wave velocity, or 24-hour BP as confounders, failed to modify the relationship between waist circumference and E/A. In conclusion, waist circumference is second only to age in the impact of the independent association with E/A in a population sample with a high prevalence of excess adiposity. This effect was not accounted for by left ventricular hypertrophy or remodeling, 24-hour BP or arterial stiffness.

2.0 Introduction

Left ventricular (LV) diastolic dysfunction identified from echocardiographic transmitral velocity measurements (E/A) and tissue Doppler assessments (E/e'), is associated with adverse cardiovascular outcomes and the development of heart failure (Aurigemma et al 2001, Schillaci et al 2002, Bella et al 2002, Redfield et al 2003, Ammar et al 2008). Several studies suggest that independent of alternative risk factors, even modest levels of obesity contribute toward the pathogenesis of an abnormal LV diastolic function (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003, Tsioufis et al 2009, Powell et al 2006, Peterson et al 2004, Wong et al 2004, Russo et al 2011). In contrast, some studies have failed to establish a relationship (Bella et al 2002, Chinali et al 2006) and others have demonstrated a relatively minor relationship of obesity to LV diastolic function (Fischer et al 2003). There are several potential explanations for differences in results between studies.

Differences in the anthropometric measures employed to index obesity, where measures of central adiposity may be more closely associated with abnormalities of LV diastolic chamber function than body mass index (BMI) (Ammar et al 2008, Tsioufis et al 2009), could explain discrepancies between studies. Moreover, in community-based studies demonstrating an independent association between adiposity and LV diastolic chamber dysfunction (Redfield et al 2003, Ammar et al 2008, Russo et al 2011), the role of LV mass (Redfield et al 2003, Ammar et al 2008), and LV relative wall thickness (Redfield et al 2003, Ammar et al 2008, Russo et al 2011) which are recognized as being associated with LV diastolic dysfunction (Schillaci et al 2002, Fischer et al 2003, Chahal et al 2010), and that of 24-hour BP and arterial stiffness, which are more closely associated with indexes of central adiposity than general or peripheral adiposity (Majane et al 2007, Majane et al 2008) have not been evaluated. To address the question of whether indices of central, general or peripheral adiposity are indeed important independent determinants of an abnormal LV diastolic chamber function at a community level, and to assess whether this effect is mediated through an impact of obesity on LV mass, LV geometry, 24-hour BP or arterial

stiffness, I therefore evaluated the relationship between a variety of indices of adiposity and E/A or E/e' in a community sample with a high prevalence of obesity (Majane et al 2007, Majane et al 2008).

2.1 Methods

2.1.1 Study group

The present study which was initiated in 2002, was approved by the University of the Witwatersrand Committee for Research in Human Subjects (approval number: M02-04-72) and was conducted according to the principles outlined in the Helsinki declaration. Participants gave informed, written consent. Nuclear families (either both parents and at least one sibling or one parent and two or more siblings) of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa. Street names and addresses of households from formal dwellings represented in the 2001 census were obtained from the Department of Home Affairs**.** These households were allocated numbers and numbers were selected from a random number generator. People residing in informal dwellings or institutions/homes were not recruited. No subjects of mixed, Asian, or European ancestry were recruited and no Khoi-San subjects were recruited. Of the 700 households approached, nuclear families from 397 housholds agreed to participate (56.7%)

Of the 671 participants enrolled in the study up until November 2006, 418 (62%) agreed to echocardiograph assessments and these original data were published in the *Am J Cardiol* (Libhaber et al 2009). Since this time and up until the end of 2011 a total sample of 678 had echocardiographic assessments. Of these, data from 23 were not included because of poor quality echocardiograph assessments and data in a further 12 participants were excluded because of poor quality transmitral velocity measurements and data in 17 participants were excluded as their left atrial diameters exceeded 2.3 cm/m^2.[17] Thus, in total,

data from 626 participants from 212 families were assessed for the purposes of this thesis. To ensure that relations between indexes of obesity and LV function were independent of haemodynamic factors other than conventional BP, I also adjusted in statistical analyses for 24-hour ambulatory BP in 437 participants with high quality echocardiograms who also had ambulatory BP recordings that met with pre-specified quality criteria (longer than 20 hours and more than 10 and 5 readings for the computation of daytime and night-time means, respectively), or pulse wave velocity (PWV) in 559 participants in whom these data could be obtained.

2.1.2 Demographic and clinical data

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

The questionnaire requested specific answers to date of birth, gender, previous medical history, including the presence of hypertension, diabetes mellitus and kidney disease, previous cardiovascular events, including stroke, myocardial infarction or heart failure, the presence of angina pectoris, prior and current drug therapy (analgesic, antihypertensive use and glucose lowering agents included), smoking status (including the number of cigarettes smoked in the past and at the present time), daily alcohol consumption (beer, traditional beer or other forms of alcohol and the daily quantity), caffeine consumption (number of cups of tea or coffee and whether they are decaffeinated and the number of cola's a day), exercise frequency and family history of hypertension. For females, menstrual history, history of pregnancies and oral contraceptive use was evaluated. Most of the questions simply required a "yes"-"no" answer, but understanding was assessed by requesting some short answers. If participants were unable to provide the name of medication taken these were obtained on a second home visit.

Height, weight, waist circumference (WC), and sub-scapular and triceps skin-fold thickness (Harpenden callipers) were measured using standard approaches and participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. Central obesity was defined as an enlarged WC (≥88 cm in women and ≥102 cm in men) (Third report of the National Cholesterol Education Program (NCEP) expert panel, 2002). Mean skin-fold thickness was calculated as the mean of sub-scapular and triceps skin-fold thickness values. Standard laboratory blood tests of renal function, liver function, haematological parameters, and percentage glycated haemoglobin (HbA_{1C}) were performed. Diabetes mellitus or abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or a glycated haemoglobin (Roche Diagnostics, Mannheim, Germany) value >6.1% (Bennett et al 2007).

2.1.3 Blood pressures

Conventional BP. High quality conventional BP measurements were obtained by a trained nurse-technician according to the European Society of Hypertension and the American Heart Association recommendations using a standard mercury sphygmomanometer (O'Brien et al 2003, Pickering et al 2005). Blood pressure was recorded to the nearest 2 mm Hg. Korotkov phases I and V were employed to identify systolic and diastolic BP respectively and care was taken to avoid auscultatory gaps. Blood pressure was measured 5 times consecutively, at least a minute apart, using appropriate sized cuffs after the subjects had rested for 5-10 minutes in the sitting position. The BP measurements were obtained between 9:00 and 14:00h. The average of the five recordings was taken as the conventional BP. The frequency of identical consecutive conventional recordings was 0.32% for systolic BP and 0.64% for diastolic BP. No conventional BP values were recorded as an odd number. Of the conventional systolic and diastolic BP readings, 31% ended on a zero (expected =20%).

Ambulatory BP. Ambulatory 24-hour BP was determined using SpaceLabs monitors (model 90207). The size of the cuff was the same as that used for conventional BP measurements. Monitors were programmed to measure 24-hour BP at 15-minute intervals from 06:00 to 22:00 hours and at 30-minute intervals from 22:00 to 06:00 hours. The average (±SD) number of ambulatory BP recordings obtained was 60.4±11.9 (range=24 to 81) for the 24-hour period.

2.1.4 Pulse wave velocity

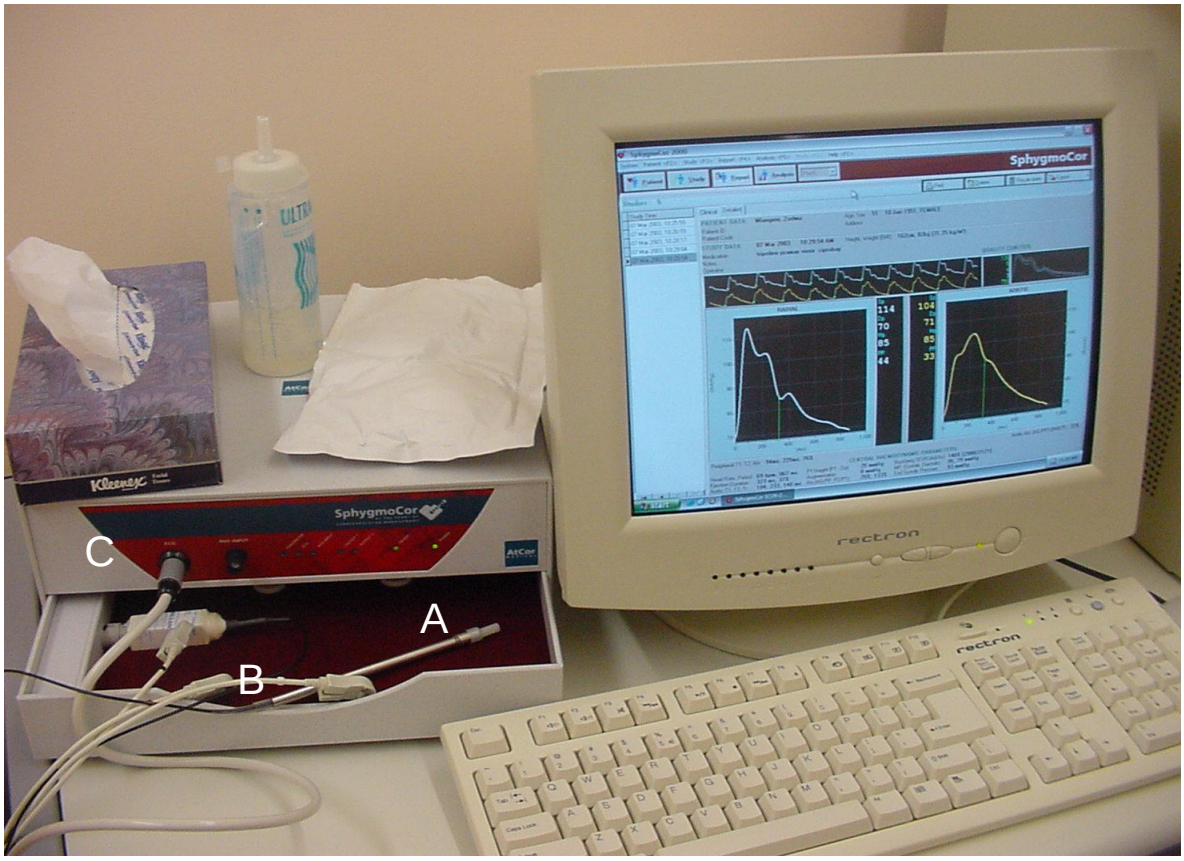
After participants had rested for 15 minutes in the supine position, arterial waveforms at the carotid and femoral artery pulses were recorded by applanation tonometry, each during an 8-second period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 9.0

software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia) (Norton et al 2012, Shiburi et al 2006) (Figure 2.1). 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. Aortic PWV was measured from sequential waveform measurements at carotid and femoral sites as previously described (Shiburi et al 2006) (Figure 2.2). Pulse wave transit time i.e. the time it takes the pulse wave to travel from the carotid to the femoral site, was determined as the difference between the times taken to generate the femoral and carotid pulse waveforms. To assess the differences in time of the generation of the femoral and carotid pulse waveforms, a single lead electrocardiogram was performed concurrently with pulse waveform sampling. The time delay in the pulse waves between the carotid and femoral sites was determined using the R wave as a fiducial point. Pulse transit time was taken as the average of 10 consecutive beats. The distance which the pulse wave travels was determined as the difference between the distance from the femoral sampling site to the suprasternal notch, and the distance from the carotid sampling site to the suprasternal notch. Aortic PWV was calculated as distance (meters) divided by transit time (seconds).

2.1.5 Echocardiography

.

Echocardiographic measurements were performed using previously described methods on the same echocardiogram (HP-5500, Palo Alto, Ca) (Norton et al 2008, Woodiwiss et al 2008, Libhaber et al 2008, Woodiwiss et al 2009). All measurements were recorded and analyzed by two experienced investigators (CL and AJW) whom were unaware of the clinical data of the participants. All participants were assessed for mitral valve abnormalities as determined using 2-dimensional and color Doppler imaging. Left ventricular



A Applanation tonometer.

B Electrocardiograph electrodes.

C SphygmoCor device.

Figure 2.1 SphygmoCor device coupled to an applanation tonometer used to determine aortic pulse wave velocity.

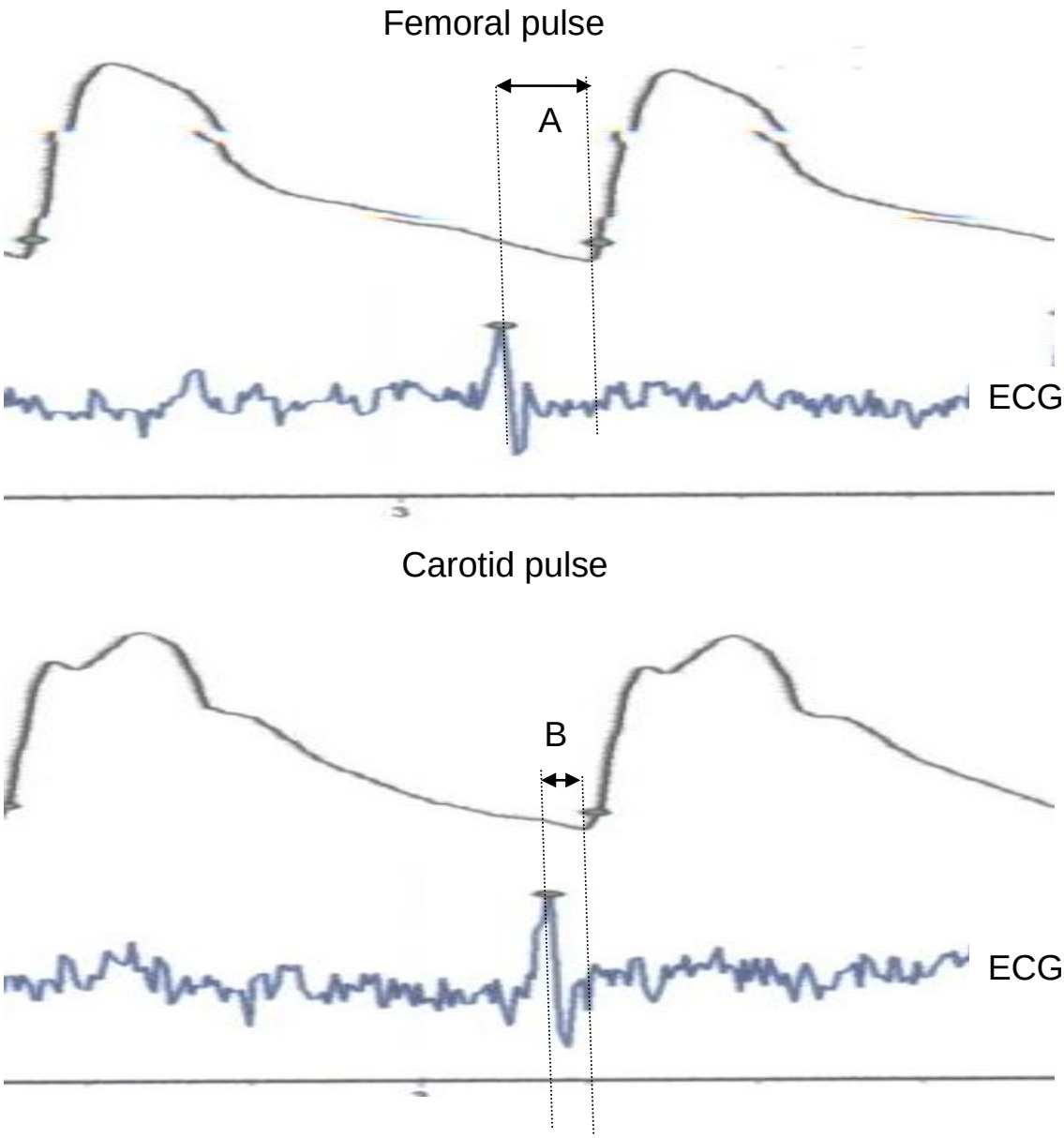


Figure 2.2. Examples of femoral and carotid artery pulse waves obtained using applanation tonometry from the same participants. Together with simultaneous electrocardiographic (ECG) recordings aortic pulse wave velocity (PWV) is calculated. The arrows indicate the time between electrical events and the arterial pressure changes in the carotid and femoral arteries used to calculate PWV. See text for a further description.

(LV) dimensions were determined using two-dimensional directed M-mode echocardiography in the short axis view and these recordings analyzed according to the American Society of Echocardiography convention (Sahn et al 1978). During recordings, the transducer was placed perpendicular to the chest wall or pointed slightly inferiorly and laterally at the end of the long axis. M-mode images were obtained perpendicular to the posterior wall and as close to the mitral leaflet as possible without images of the mitral leaflet appearing. The interventricular septal wall thickness (IVS) at end diastole and end systole, the posterior wall thickness (PWT) at end diastole and end systole and the end diastolic and end systolic internal dimensions of the left ventricle were measured only when appropriate visualization of both the right and the left septal surfaces occurred and where the endocardial surfaces of both the septal and posterior wall were clearly visible. Figure 2.3 shows a representative M-mode image employed to assess left ventricular mass and function.

In each participant, left ventricular diastolic function was assessed from a pulsed wave Doppler examination of the mitral inflow at rest and myocardial tissue Doppler imaging of the septal and the lateral wall of the left ventricle in 212 participants (Tissue doppler imaging software was unavailable in South Africa at the time the study was initiated in 2002). Pulse wave Doppler recordings of transmitral velocity were obtained with the sample volume at the tip of the mitral valve in the apical 4-chamber view. Figure 2.4 shows representative images of transmitral velocity measurements obtained during the early (E) and late (atrial-A) period of left ventricular diastolic inflow. Left ventricular diastolic function was assessed from E/A ratio. Tissue Doppler recordings were obtained from the apical 4-chamber view with the Doppler sample volume positioned at the lateral and septal wall, close to the mitral annulus. Figure 2.5 shows a representative image of myocardial tissue Doppler measurements obtained during the early (e') and late (atrial-a') period of left ventricular diastole. Analysis was conducted on the average of the e'/a' obtained from the lateral wall and septum.

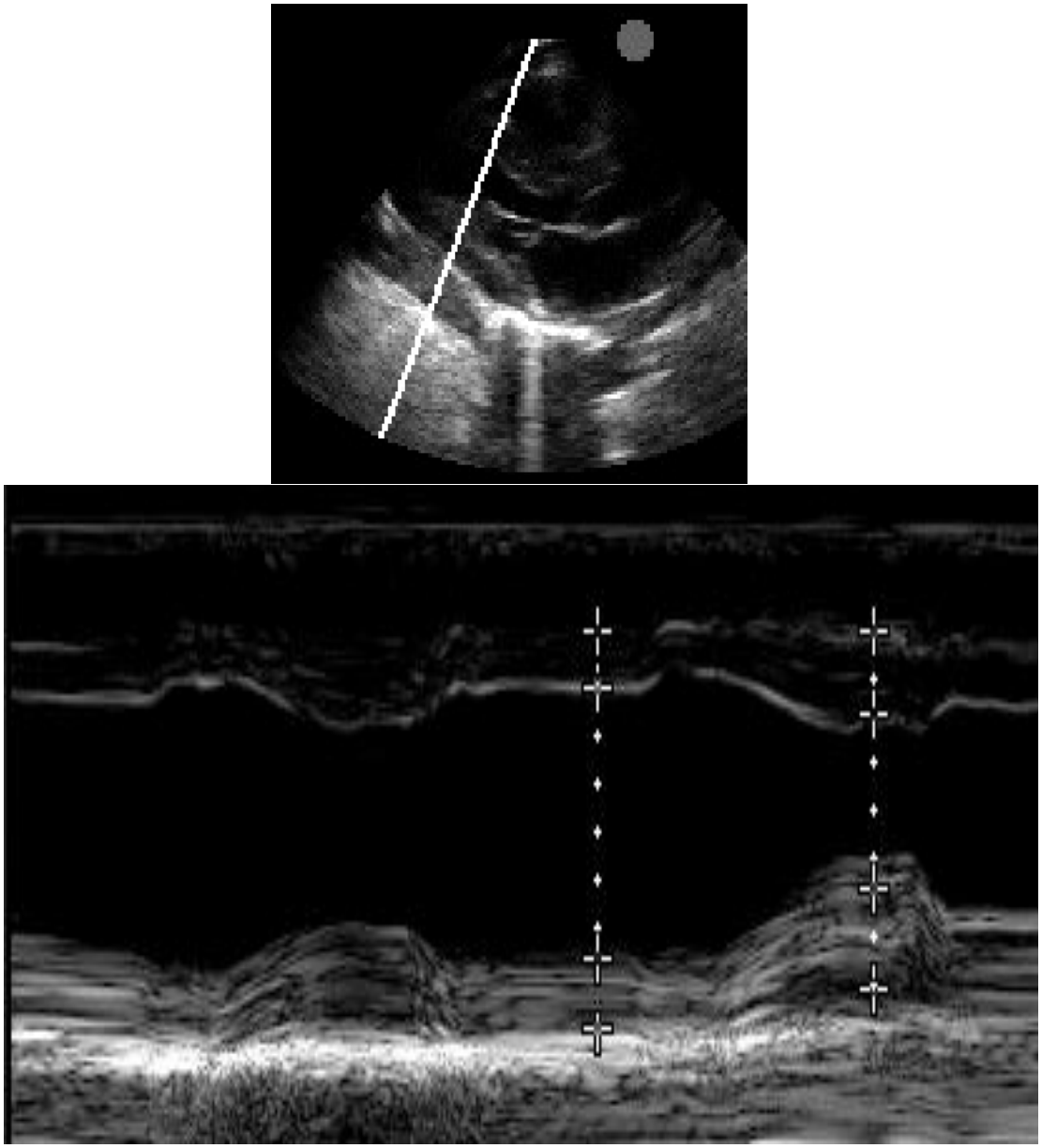


Figure 2.3. A two-dimensional guided (upper panel) M-mode echocardiographic image (lower panel) derived from a Hewlett Packard model 5500 utilised to assess left ventricular dimensions and function.

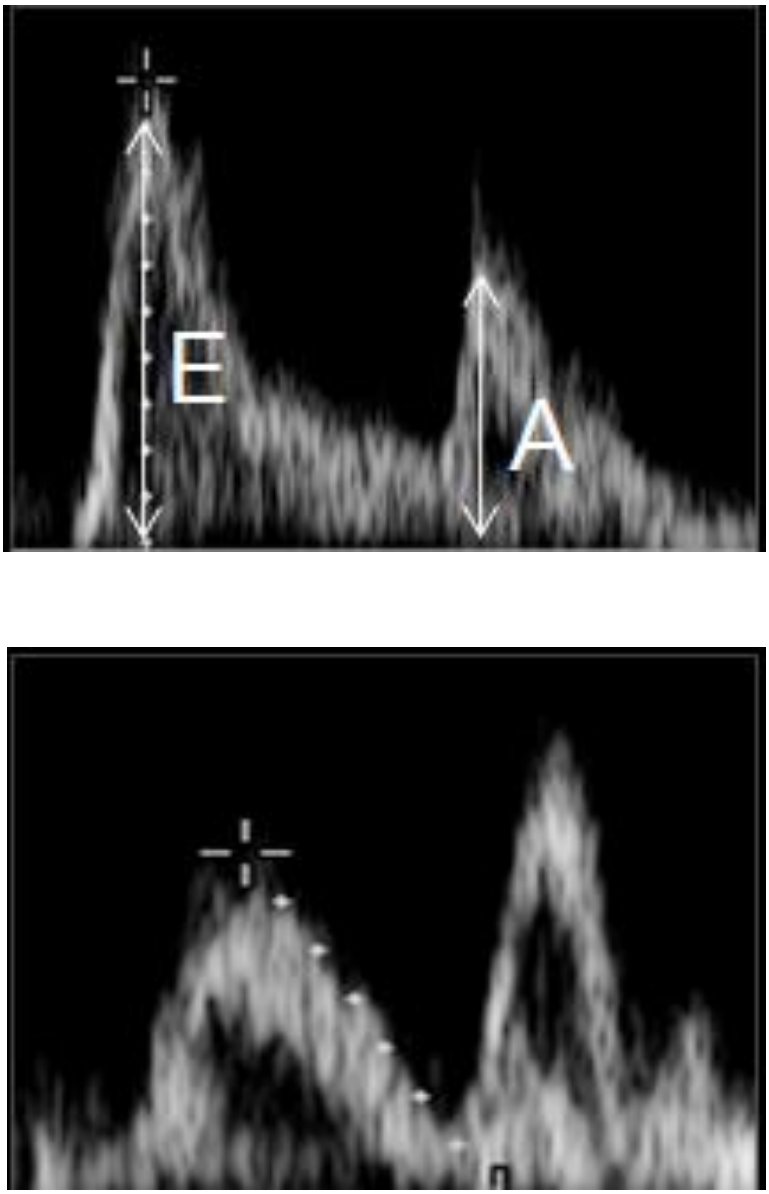


Figure 2.4. Transmitral Doppler patterns obtained from two participants showing a normal early (E)-to-late (atrial)(A) transmitral flow velocity ratio (E/A) (upper panel) and a reduced E/A (lower panel). Dotted lines in the upper panel show measurements obtained for the E wave amplitude.

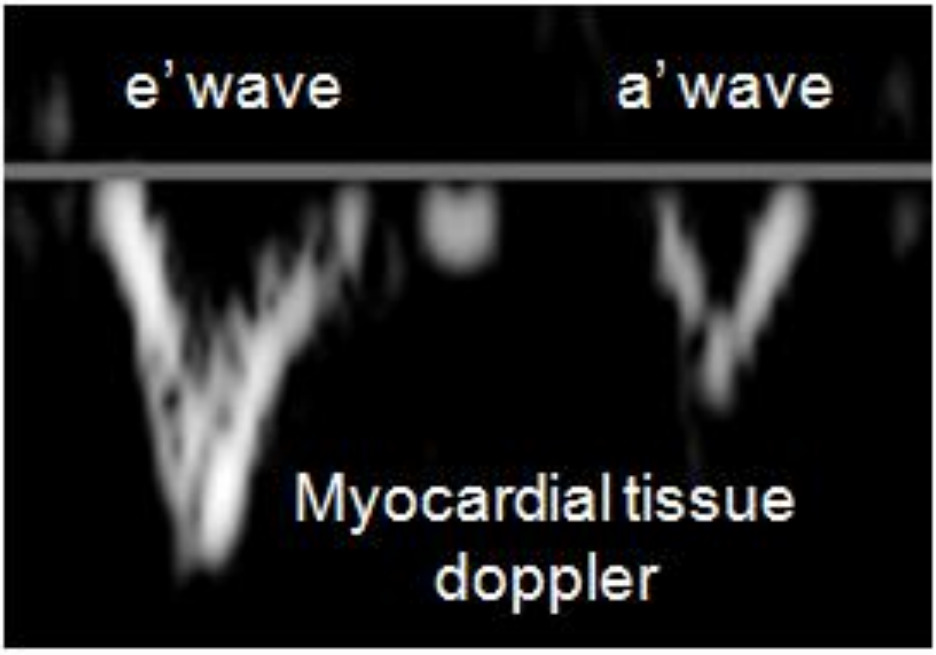


Figure 2.5. Myocardial tissue Doppler patterns obtained from a participant showing normal early (e') and late (atrial)(a') myocardial tissue lengthening.

Left ventricular end diastolic and systolic volumes were determined using both the Teichholz (Teichholz et al 1976) and the Z-derived (de Simone[c] et al 1996) methods. Left ventricular ejection fraction (EF) was calculated as [(LV end diastolic volume-LV end systolic volume)/ LV end diastolic volume] x 100. An abnormal systolic function was defined as an LV EF of ≤50%, with a moderate-to-severe reduction in LV EF defined as ≤40% (Redfield et al 2003). Left ventricular (LVM) mass was derived according to an anatomically validated formula (Devereux et al 1986) (LVM = 0.8 x [1.04 (LVEDD + IVS +PWT) ^{3} – (LVEDD) ^{3}] + 0.6g) and indexed to height$^{2.7}$ (LVM index, LVMI). Left ventricular relative wall thickness was calculated as (LV diastolic posterior wall thickness x2)/LV end diastolic diameter (Ganau et al1992). Left ventricular mean wall thickness was determined from the mean of LV septal and posterior wall thickness. Left ventricular hypertrophy (LVH) was defined as a LVMI >51 g/m$^{2.7}$ for both women and men (Nunez et al 2005).

Intra-observer variability studies were conducted on 29 subjects on whom repeat echocardiographic measurements have been performed within a two week period of the initial measurements. The Pearson's correlation coefficients for LV end diastolic diameter, septal wall thickness and posterior wall thickness were 0.76, 0.94 and 0.89 (all $p<0.0001$) respectively, and the variances (mean % difference ± SD) were 0.12±5.95%, -0.77±4.47% and 0.67±5.57% respectively. In addition, no significant differences between repeat measurements were evident on paired t-test analysis ($p=0.99$, $p=0.42$ and $p=0.48$ respectively). The Pearson's correlation coefficients for E and A were 0.92 and 0.77 (both $p<0.0001$) respectively, and the variances (mean % difference ± SD) were -1.48±12.3% and -0.94±16.69% respectively. No significant differences between repeat measurements were evident on paired t-test analysis ($p=0.41$, $p=0.94$ respectively).

Inter-observer variability studies were conducted on 26 participants on whom the two echocardiographers involved in obtaining measurements performed echocardiography on the same participants whilst blinded to each others measurements. The Pearson's correlation coefficients for LV end diastolic diameter, septal wall thickness and posterior wall thickness were 0.96, 0.84 and 0.88 (all $p<0.0001$) respectively, and the variances (mean %

difference ± SD) were 0.49±2.71%, -1.69±7.19% and 0.23±5.89% respectively. In addition, no significant differences between measurements were evident on unpaired t-test analysis (p=0.38, p=0.26 and p=0.85 respectively). The Pearson's correlation coefficients for E and A were 0.71 and 0.86 (both p<0.0001) respectively, and the variances (mean % difference ± SD) were 4.76±16.03% and 3.58±12.13% respectively. No significant differences between repeat measurements were evident on unpaired t-test analysis (p=0.16 for both).

2.1.6 Data analysis

Database management and statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Descriptive data are reported as mean±SD. Independent relations between indexes of adiposity and diastolic (E/A, or E/e') or systolic (LV ejection fraction) chamber function were determined from multivariate linear regression analysis with adjustments for age, sex, conventional systolic or diastolic BP (or 24-hour BP or PWV), diabetes mellitus or an HbA1c>6.1%, antihypertensive treatment, regular tobacco or alcohol intake, total/HDL cholesterol, pulse rate and either LVMI or relative wall thickness (calculated from LV septal plus posterior wall thickness/LV end diastolic diameter). Partial correlation coefficients between indexes of obesity and E/A were determined by assessing these relations after adjusting for covariates. Probability values were further adjusted for non-independence of family members using the method of maximum likelihood as implemented by the mixed procedure as defined in the SAS package. The mixed model contains both fixed effects (all phenotypic data) parameters and random-effects (familial relationships) parameters. To compare the magnitude of the impact of different variables on E/A, standardized β-coefficients were determined from stepwise linear regression analysis and these coefficients compared using a one way analysis of variance.

2.2 Results

2.2.1 Participant characteristics

Table 2.1 gives the demographic, clinical and haemodynamic characteristics of the participants with E/A data and the characteristics of the participants without E/A data. No differences were noted between these two groups. More women than men participated. In general the group had a high BMI, and a high proportion of participants were overweight or obese. A high proportion of participants were hypertensive with ~54% of hypertensives receiving treatment and only ~36% of hypertensives controlled to target BP values. Approximately a quarter of the participants had diabetes mellitus or an impaired blood glucose control. None of the participants had mitral valve abnormalities. ~20% of men and ~23% of women had LVH. Approximately 12% (n=74) had mild diastolic chamber dysfunction or impaired relaxation with an E/A ≤0.75, and ~30% (n=189) severe diastolic chamber dysfunction with an E/A≥1.50. Only 20 participants had a reduced LV ejection fraction (<50%) and none had moderate-to-severe reductions in LV ejection fraction. No differences were noted between participants with tissue Doppler assessments as compared to those without (see Appendix, Table 1). In this group the mean±SD e' wave velocity was 11.59±3.80 cm/sec, a' wave velocity was 8.10±2.96 cm/sec, e'/a' was 1.67±0.87 and E/e' was 6.86±3.46.

2.2.2 Bivariate relationships between indices of adiposity and left ventricular function.

Figure 2.6 shows unadjusted correlations and Pearson's correlations coefficients between some indices of adiposity and either E/A or LV ejection fraction. A strong inverse correlation between waist circumference and E/A, and between BMI and E/A was noted (Figure 2.6). Moreover, waist-to-hip ratio ($r=-0.41$, $p<0.0001$) and mean skin-fold thickness

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

	With	Without
Number	626	565
Women	65%	65.5%
Age (years)	43.0±18	44.0±19
Body mass index (kg/m^2)	29.3±7.6	29.6±8.5
Waist circumference (cm)	90.3±16.6	90.2±16.8
Waist-to-hip ratio	0.84±0.10	0.83±0.10
Subscapular skin-fold thickness (cm)	2.37±1.22	2.41±1.31
Triceps skin-fold thickness (cm)	1.78±1.05	1.60±1.03
Mean skin-fold thickness (cm)	2.07±1.03	2.01±1.06
Overweight/obese (%)	23.8/42.5	22.1/43.0
Central obesity (%)	44.7	42.1
Hypertension (%)	43.0	41.6
Receiving antihypertensives 9%)	23.5	23.0
Diabetes mellitus or glycated haemoglobin >6.1% (%)	27.0	23.4
Regular smoking (%)	14.1	15.9
Regular alcohol (%)	20.1	22.3
Conventional systolic BP/ diastolic BP (mm Hg)	129±22/84±13	130±23/85±13
24-hour systolic BP/diastolic BP (mm Hg)	119±15/73±10 (n=437)	118±15/73±10 (n=359)
Pulse wave velocity (m/sec)	6.13±2.75 (n=559)	6.73±2.52 (n=482)
LV mass (g)	155.5±50.4	-
LV mass indexed for height$^{2.7}$ (g/m$^{2.7}$)	42.8±14.2	-
LV hypertrophy (%)	21.7	-
E wave velocity (cm/s)	77.4±25.2	-
A wave velocity (cm/s)	64.5±21.7	-
E/A	1.30±0.49	-
LV ejection fraction (%)	66.9±8.7	-

BP, blood pressure; LV, left ventricular; E, early transmitral velocity; A, late (atrial) transmitral velocity.

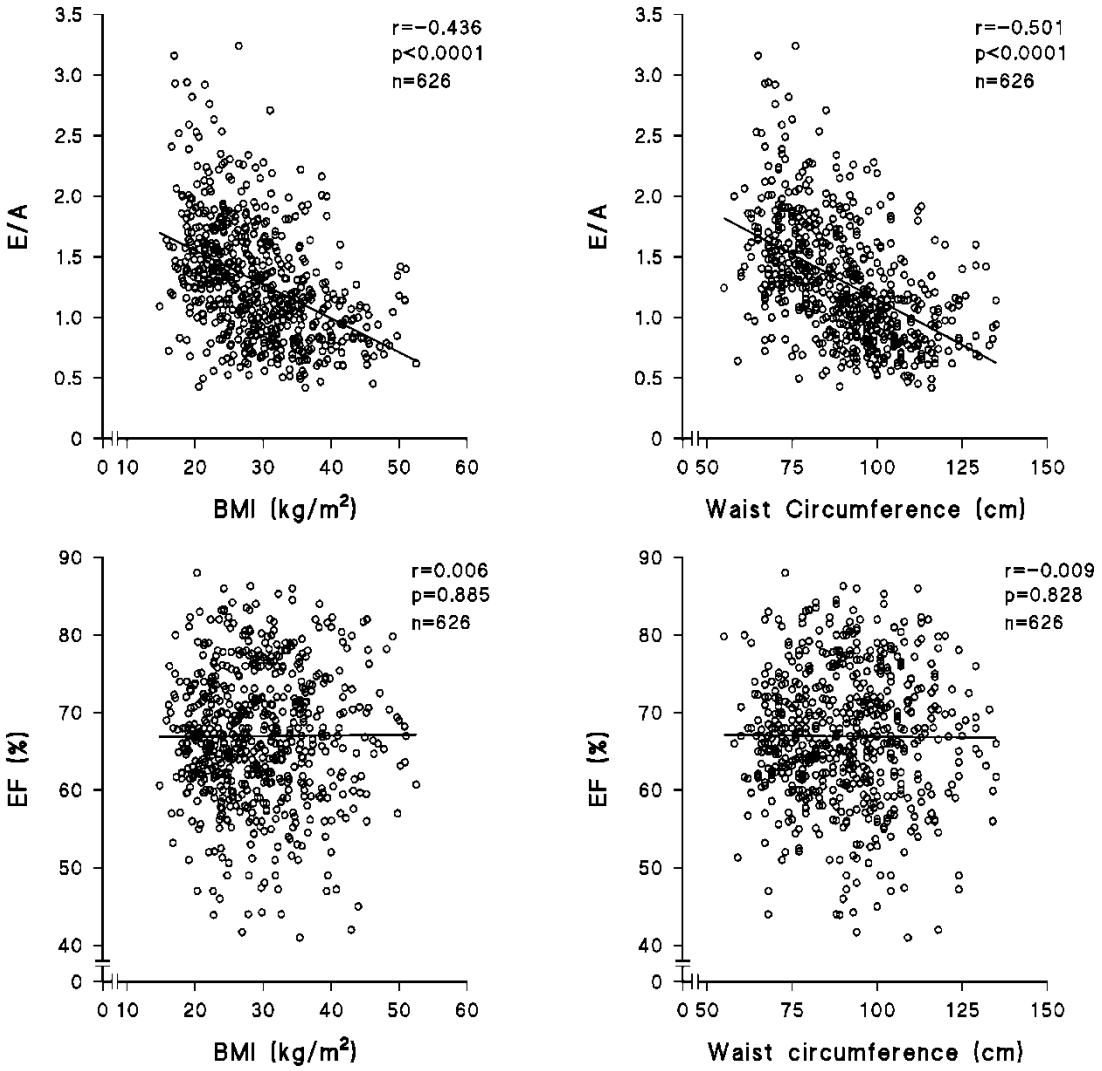


Figure 2.6. Bivariate relationships between indexes of adiposity and left ventricular early-to-late (atrial) transmitral velocity (E/A) and left ventricular ejection fraction (EF) in the study sample. BMI, body mass index.

(r=-0.26, p<0.0001) were also inversely correlated with E/A. No relationship between either waist circumference or BMI and LV ejection fraction were noted (Figure 2.6). Similarly, neither waist-to-hip ratio nor mean skin-fold thickness were correlated with LV ejection fraction (data not shown).

Strong inverse correlations between waist circumference and both E/A (r=-0.46, p<0.0001, n=212) and e'/a' (r=-0.52, p<0.0001, n=212) were noted in the cohort with tissue Doppler assessments. Moreover, BMI (r=-0.48, p<0.0001, n=212), mean skinfold thickness (r=-0.36, p<0.0001, n=212) and waist-to-hip ratio (r=-0.44, p<0.0001, n=212) were inversely correlated with e'/a'. Univariate direct correlations between waist circumference (r=0.25, p<0.0005), BMI (r=0.25, p<0.0005, n=212), waist-to-hip ratio (r=0.26, p=0.0001, n=212) or mean skinfold thickness (r=0.17, p<0.0001, n=212) and E/e' were also noted.

2.2.3 Factors other than adiposity indices related to left ventricular diastolic function

Factors other than adiposity indexes associated with E/A included age (r=-0.67, p<0.0001), male gender (r=-0.12, p<0.005), conventional systolic (r=-0.46, p<0.0001) and diastolic (r=-0.35, p<0.0001) BP, LVMI (r=-0.36, p<0.0001), relative wall thickness (r=-0.31, p<0.0001), diabetes mellitus or an HbA1c>6.1% (r=-0.35, p<0.0001), and antihypertensive treatment (r=-0.39, p<0.0001). Neither pulse rate, regular tobacco intake, or regular alcohol intake were associated with E/A. In addition, 24-hour systolic (r=-0.33, p<0.0001), and diastolic (r=-0.32, p<0.0001) BP, and PWV (r=-0.48, p<0.0001) were inversely correlated with E/A.

2.2.4 Multivariate adjusted relationships between adiposity indices and left ventricular diastolic function.

Figure 2.7, upper panel shows the partial correlation coefficients (correlations between adiposity indices and E/A obtained after adjustments for additional variables) for the

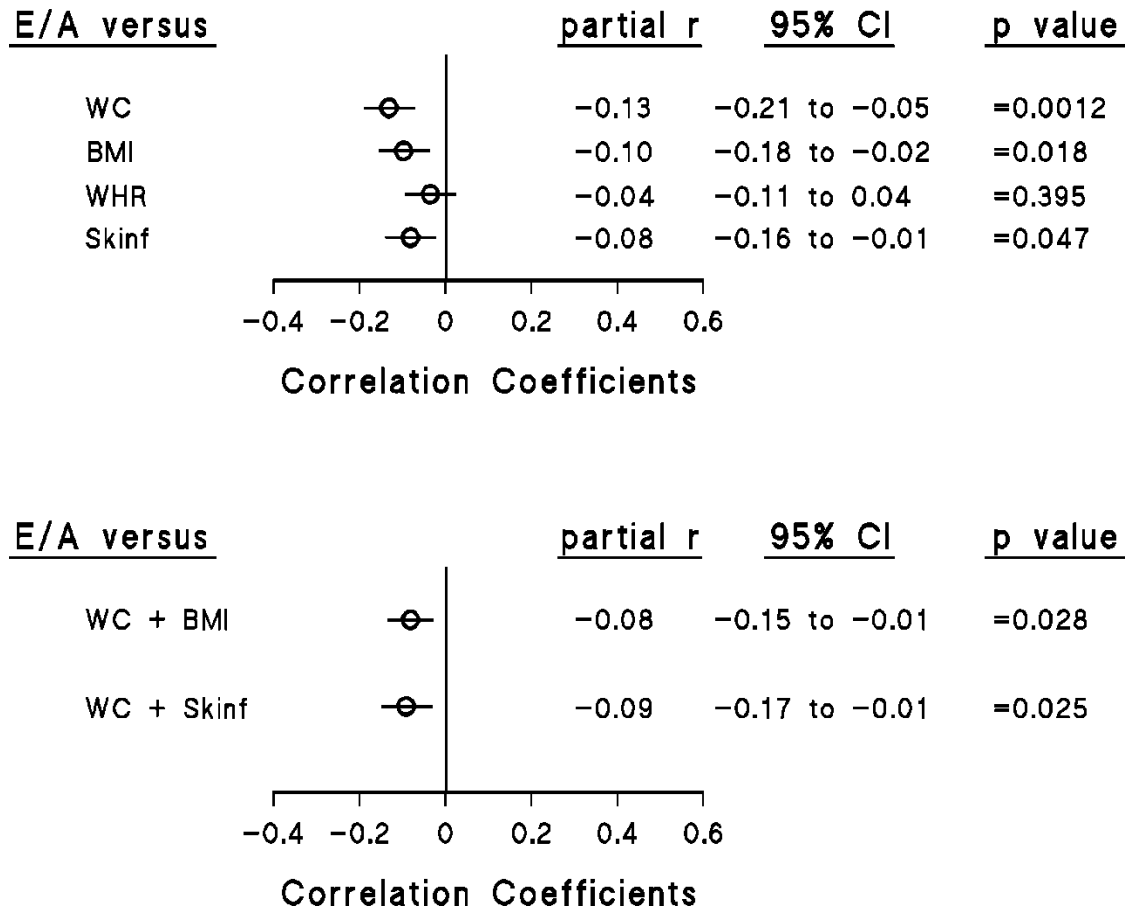


Figure 2.7. Partial correlations coefficients and 95% confidence intervals of the multivariate adjusted relationships between indices of adiposity and left ventricular early-to-late (atrial) transmitral velocity (E/A) in 626 participants. The upper panel shows adiposity indices considered separately in each model. The lower panel considers WC effects with additional adjustments for BMI, or Skinf. WC, waist circumference; BMI, body mass index; WHR, waist-to-hip ratio; Skinf, mean skin-fold thickness. Adjustments were for age, sex, conventional diastolic BP, diabetes mellitus or a glycated haemoglobin>6.1%, antihypertensive treatment, regular tobacco or alcohol intake, pulse rate and LV mass index. Probability values were further adjusted for non-independence of family members.

independent relations between different indices of adiposity and E/A with LVMI included in the regression model. Waist circumference, BMI and mean skinfold thickness were independently and inversely correlated with E/A. In contrast waist-to-hip ratio showed no significant independent relations with E/A. With LV relative wall thickness rather than LVMI included in the regression model, waist circumference (partial r=-0.15, p<0.0005), BMI (partial r=-0.12, p<0.005) and mean skinfold thickness (partial r=-0.085, p<0.05) remained independently and inversely correlated with E/A.

Figure 2.7, lower panel shows the independent relations between waist circumference and E/A after adjustments for either BMI, or mean skin-fold thickness with LVMI included in the regression models. The relationship between waist circumference and E/A persisted following adjustments for either BMI, or mean skin-fold thickness. Similarly, with LV relative wall thickness rather than LVMI included in the regression model, waist circumference was associated with E/A independent of BMI (partial r=-0.08, p=0.029) or skin-fold thickness (partial r=-0.10, p=0.014). In contrast, the relationships between BMI and E/A (partial r=-0.001, p=0-.97) and between skinfold thickness and E/A (partial r=-0.004, p=0.92) were abolished following adjustments for waist circumference.

With adjustments for confounding variables including LVMI in the model, in the group with tissue Doppler assessments waist circumference (partial r=-0.22, p<0.005), and BMI (partial r=-0.21, p<0.005, n=212), but neither mean skinfold thickness (partial r=-0.13, p=0.06, n=212) nor waist-to-hip ratio (partial r=-0.13, p=0.06, n=212) were independently and inversely correlated with e'/a'. Replacing LVMI with LV relative wall thickness in the model, waist circumference (partial r=-0.22, p<0.005, n=212), and BMI (partial r=-0.22, p<0.005) but neither mean skinfold thickness (partial r=-0.13, p=0.06), nor waist-to-hip ratio (partial r=-0.13, p=0.06) were similarly independently and inversely correlated with e'/a'. The strength of the multivariate relationship between waist circumference and E/A in the subgroup with tissue Doppler imaging (partial r=-0.16, p=0.05) was similar to that noted between waist circumference and e'/a' (comparison of partial r values using Z statistics). Despite bivariate relationships between adiposity indices and E/e' (see section 2.2.2 above),

in multivariate analysis these relationships did not achieve significance (waist circumference vs. E/e'; partial r=0.06, p=0.43, BMI vs. E/e'; partial r=0.05, p=0.51, waist-to-hip ratio vs. E/e'; partial r=0.11, p=0.12, mean skinfold thickness vs E/e'; partial r=-0.05, p=0.53).

With adjustments for confounders and LVMI in the model, the relationship between waist circumference and e'/a' did not achieve significance following further adjustments for BMI (partial r=-0.11, p=0.12, n=212). The relationship between BMI and e'/a' was abolished following further adjustments for waist circumference (partial r=-0.03, p=0.66, n=212).

2.2.5 Comparison of the impact of adiposity indices versus alternative factors on left ventricular diastolic function.

Table 2.2 shows a comparison of the standardized β-coefficients for the independent relations between variables associated with E/A in multivariate regression models. The relations between waist circumference and E/A were similar irrespective of whether LVMI was (standardized β-coefficient=-0.111±0.038, p=0.0036) or was not (standardized β-coefficient=-0.123±0.037, p=0.001) included in the regression model. Similar results were noted with systolic as opposed to diastolic BP in the regression model (waist circumference versus E/A adjusted for confounders and systolic BP: standardized β-coefficient=-0.136±0.038, p=0.0004). Other factors independently associated with E/A included age, diastolic BP and pulse rate (Table 2.2). The magnitude of the effect of waist circumference on E/A was comparable with the effect of BP on E/A and second only to the magnitude of the effect of age on E/A (Table 2.2).

2.2.4 Multivariate adjusted relationships between adiposity indices and left ventricular diastolic function with adjustments for additional haemodynamic factors.

Table .2.3 shows the factors independently associated with E/A in multivariate regression models with 24-hour diastolic BP or PWV included in the regression models.

Table 2.2. Independent associations with left ventricular E/A in multivariate regression models and comparison of the impact of these variables on E/A in the study group (n=626).

Variable	Standardized β-coefficient±SEM	p value for relationship
Age	-0.54±0.04*	**<0.0001**
Waist circumference	-0.11±0.04	**=0.0036**
Diastolic blood pressure	-0.14±0.03	**<0.0001**
Sex	-0.05±0.03	=0.091
Treatment for hypertension	-0.01±0.04	=0.809
Diabetes mellitus or glycated hemoglobin>6.1%	-0.03±0.03	=0.316
Left ventricular mass index	-0.05±0.03	=0.093
Pulse rate	-0.07±0.03	**=0.023**
Regular tobacco	0.03±0.03	=0.340
Regular alcohol	-0.00±0.03	=0.996

Probability values were further adjusted for non-independence of family members. Significant probability values are indicated in bold. Model r^2=0.51, p<0.0001.* p<0.001 as compared to standardized β-coefficients for waist circumference and diastolic blood pressure.

Table 2.3. Independent associations with left ventricular E/A in a multivariate adjusted regression model with ambulatory diastolic blood pressure (BP) or carotid-femoral pulse wave velocity included in the models.

	24 hour DBP included in model		PWV included in model	
	n=437		n=559	
	Standardized β-coefficient±SEM	p value	Standardized β-coefficient±SEM	p value
Age	-0.53±0.05	<0.0001	-0.52±0.05	<0.0001
24-hour diastolic BP	-0.13±0.04	=0.0004	-	-
Pulse wave velocity	-	-	0.08±0.04	=0.070
Waist circumference	-0.14±0.05	=0.0029	-0.13±0.04	=0.0013
Sex	-0.03±014	=0.450	-0.03±0.04	=0.406
Treatment	-0.003±0.04	=0.937	-0.005±0.04	=0.890
Diabetes mellitus or glycated hemoglobin>6.1%	-0.002±0.04	=0.953	0.01±0.04	=0.692
LV mass index	-0.04±0.04	=0.271	0.05±0.04	=0.155
Pulse rate	-0.05±0.03	=0.164	-0.07±0.03	=0.018
Regular tobacco	-0.06±0.04	=0.140	0.02±0.03	=0.541
Regular alcohol	-0.01±0.04	=0.748	-0.01±0.03	=0.689

Probability values were further adjusted for non-independence of family members. Significant probability values are indicated in bold. Model r^2=0.58 ($p<0.0001$) for model with 24-hour diastolic BP included and model r^2=0.60 ($p<0.0001$) for model with PWV included.

Even with these factors included in the models, waist circumference was independently associated with E/A. Replacing 24-hour diastolic BP with 24-hour systolic BP still showed waist circumference to be independently associated with E/A (standardized β-coefficient=-0.144±0.045, p=0.0017).

2.3 Discussion

The main findings of the present study are that in a randomly selected community sample with a high prevalence of excess adiposity, waist circumference, BMI and skinfold thickness were independently associated with a reduced E/A, and waist circumference was second only to age and at least equivalent to diastolic BP in the magnitude of the effect. Waist circumference and BMI were also independently associated with myocardial diastolic function, as determined from the tissue Doppler index e'/a'. In contrast to the relationship between waist circumference and E/A persisting after adjustments for alternative adiposity indices, neither BMI nor skinfold thickness retained an independent relationship with E/A after adjustments for waist circumference. The independent relation between waist circumference and E/A also largely persisted with the inclusion of either LV mass index, LV relative wall thickness, 24-hour BP or PWV (an index of arterial stiffness) in the regression models, thus suggesting that these factors are unlikely to explain the major effect of waist circumference on LV diastolic function.

The data reported on in the present study contribute toward our understanding of the importance of excess adiposity as a determinant of LV diastolic abnormalities at a community level. In this regard, the present study supports the findings of other studies with large study sizes (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003, Tsioufis et al 2009, Russo et al 2011). However, in these studies, these relationships were either not adjusted for confounders (Redfield et al 2003); were modest at best (Redfield et al 2003, Fischer et al 2003); were conducted in hypertensives only (Tsioufis et al 2009) where the residual confounding effects of hypertension cannot be eliminated; were conducted in a

population sample of middle-aged to elderly individuals only (Redfield et al 2003, Ammar et al 2008) where the residual confounding effects of age on diastolic function cannot be eliminated; were not adjusted for LVMI (Redfield et al 2003, Ammar et al 2008); or were published after (Russo et al 2011) the results of the present study (Libhaber et al 2009). Thus, to the best of my knowledge, the present study was the first to provide a reflection of the independent impact of excess adiposity on LV diastolic function at a community level.

The present and prior (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003, Tsioufis et al 2009, Russo et al 2011) studies do not support the findings of other (Bella et al 2002, Chinali et al 2006, De Simone et al 2011) studies with large study sizes which failed to demonstrate an independent relationship between indices of adiposity and LV diastolic dysfunction. The lack of independent relationship between adiposity and E/A in adolescents (Chinali et al 2006) may relate to the younger age of the participants as compared to other studies. Nevertheless, the presence of an abnormal E/A in adult participants with a reduced as opposed to increased BMI is difficult to explain (Bella et al 2002) unless differences in loading conditions influenced the outcome of this study. It is possible that the lack of rtelationship between BMI and E/A in some studies (Bella et al 2002, Chinali et al 2006, De Simone et al 2011), could be explained by a stronger relationship between indices of central adiposity rather than BMI and abnormalities of diastolic function. In this regard, in agreement with prior studies that have demonstrated a less robust relationship between BMI and abnormalities of diastolic function (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003) as compared to that between indices of central adiposity and abnormalities of diastolic function (Ammar et al 2008, Tsioufis et al 2009), in the present study no significant independent relationship between BMI and E/A was noted after adjustments for waist circumference, despite persistence of the independent relationship between an index of central adiposity (waist circumference) and E/A after adjustments for alternative indices of adiposity (BMI and skinfold thickness). However, at variance to a previous study (Ammar et al 2008), in the present study I failed to show an independent relationship between waist-to-hip ratio and E/A. Although an explanation for the differences between studies is not

apparent, such disparities could be attributed to distinct characteristics of the study populations.

The results of the present study indicate that at a community level, waist circumference is second only to age and equivalent to BP in the magnitude of the effect on E/A. Although prior to the publication of the present study (Libhaber et al 2009), an alternative study performed in the general population had reported on independent associations between indices of central obesity and abnormalities of LV diastolic function (Ammar et al 2008), the relative impact of central adiposity on E/A as compared to alternative cardiovascular risk factors, was unclear. In the present study I show that the independent impact of waist circumference on E/A is equivalent to that of both conventional and 24-hour BP, the latter being a BP measurement that may better predict target organ changes.

Whether the independent associations between indices of central or general obesity and abnormalities of LV diastolic function previously reported on in large study samples and at a population or community level (Redfield et al 2003, Ammar et al 2008, Tsioufis et al 2009) reflect an effect of obesity-induced increases in LVMI or concentric LV remodelling, factors that are strongly associated with diastolic dysfunction (Fischer et al 2003, Chahal et al 2010, Schillaci et al 2002), is uncertain. Previous studies conducted in large study samples had indeed demonstrated that with adjustments for LVH, only marginal associations between adiposity indices and LV diastolic function exist (Fischer et al 2003). In the present study I show that the strength of the independent relations between indices of adiposity and E/A are retained after adjustments for either LVMI or LV relative wall thickness. I therefore provide the first evidence in a relatively large community-based sample to suggest that LVM and geometry may contribute only to a minor extent to the pathogenesis of obesity-induced LV diastolic abnormalities. Although a subsequent larger population-based study has similarly demonstrated relations between excess adiposity and diastolic dysfunction independent of LVMI (Russo et al 2011), this study did not report on adjustments for relative wall thickness. However, as obesity was not associated with an increased relative wall

thickness in that study (Russo et al 2011), both the present (published in 2009, Libhaber et al 2009) and this prior study (Russo et al 2011) may be consistent with each other.

As these measurements were unavailable to me at the time of initiating the present study, in the present study myocardial tissue Doppler assessments of diastolic function were only conducted in a subgroup of the study sample. Hence, I cannot report on the relationship between adiposity indices and pseudonormal filling patterns, and thus relationships between adiposity indices and LV diastolic dysfunction. Nevertheless, in those participants who had tissue Doppler imaging, the strength of the relationship between e'/a' was similar to that for E/A. Although E/e', an index of left atrial driving force and hence left ventricular filling pressures, was not independently associated with adiposity indices, this may reflect a false negative finding due to the small study sample which had tissue Doppler imaging (n=212). Hence, at this point I cannot comment on whether abnormalities in LV diastolic function associated with excess adiposity are sufficiently severe that they translate into increases in LV filling pressures. Further work is required in this regard.

Potential explanations for the independent relationship between adiposity and an abnormal LV diastolic function, could include undiagnosed obesity-induced obstructive sleep apnoea, insulin resistance as suggested by some small case-control studies (Lind et al 1995, Mureddu et al 1998, Watanabe et al 1999, Wong et al 2004, Bajraktari et al 2006, Sliem et al 2011, Utz et al 2011) and one large study which did not evaluate relationships beyond adiposity indices (Hwang et al 2011), free fatty acid-induced lipotoxicity (Leichman[b] et al 2006), inflammatory changes (Wu et al 2012), obesity-associated myocardial apoptosis, and a reduced mitochondrial biogenesis and function (Niemann et al 2011) and excess sympathetic nervous system activation (Lambert et al 2010). However, not all studies support a role for insulin resistance in mediating decreases in LV diastolic function (Wu et al 2012, Wada et al 2010, Lambert et al 2010). Nevertheless, these were also small studies subject to false negative results or a selection bias and hence further large population or community-based studies; prospective studies; and intervention studies are required to evaluate these potential mechanisms. In this regard, as part of the present thesis I explored

the role of insulin resistance in mediating abnormalities of LV diastolic function beyond adiposity indices in a large cohort of the present community-based sample. These data and the implications thereof are presented in chapter 3.

With respect to the clinical implications of the present findings, obesity-induced LV diastolic abnormalities may represent a progressive preclinical condition that contributes to obesity-induced heart failure (Chen et al 1999, He et al 2001, Johansson et al 2001, Wilhelmsen et al 2001, Kenchaiah et al 2002, 2009, Ingelsson et al 2005a and 2005b, Nicklas et al 2006, Bahrami et al 2008, Spies et al 2009). Indeed, LV diastolic dysfunction is associated with the development of heart failure (Aurigemma et al 2001, Ammar et al 2008). It is important to note that significant weight loss can result in an increase in E/A (Willens et al 2005, Hsuan et al 2010).

The present study has several strengths and limitations. The strengths of the study include the use of a relatively large unselected community sample, thus limiting the probability of a selection bias and false positive findings. Second, the use of ambulatory BP and arterial stiffness assessments to adjust for the impact of haemodynamic factors on the relationships between waist circumference and diastolic function in a cohort of participants is also a strength of the present study. Thus, the chances of the independent relationship noted between indices of adiposity and E/A being attributed to inappropriate estimates of BP or haemodynamic factors being employed are likely to have been reduced. Second, I evaluated relations between indices of adiposity and E/A or e'/a' using BP, E/A and e'a' as continuous rather than dichotomous traits, thus improving the probability of a positive outcome.

The limitations of the study are first the cross-sectional rather than prospective nature of the study design. Thus, the relationships demonstrated may not reflect cause and effect. Second, I did not measure pulmonary venous reverse flow and mitral inflow during the peak of the valsalva maneuver. Moreover, as tissue Doppler imaging was only available on a subgroup of participants, as indicated in the aforementioned discussion I could not identify the presence of pseudonormal filling patterns. Thus, I did not assess the relationship

between adiposity indices and the presence of diastolic dysfunction reported as a discrete trait. Third, the limited proportion of male participants recruited for the study prevented sex-specific analyses, and thus the effect reported on in the present study may be restricted to females as previously suggested by other studies (Tsioufis et al 2009). Furthermore, an additional limitation of the present study is that the LV ejection fraction was measured with echocardiography whilst magnetic resonance imaging (MRI) measurements of systolic function have been demonstrated to be more sensitive for predicting cardiovascular events (Mewton et al 2013). It is therefore possible that we may have demonstrated stronger relationships between obesity indices and LV ejection fraction if magnetic resonance imaging had been employed. Last, relatively weak partial r values were noted for relationships between adiposity indices and E/A, a finding that must be interpreted with caution. This may reflect an overall weak relationship between obesity and E/A, or an inability to appropriately account for all confounders or to exclude the impact of co-linearity between adjustors in multivariate models. Only intervention studies are likely to reveal the actual magnitude of the effect of obesity on E/A if indeed this relationship is cause and effect.

In conclusion, the results of the present study suggest that obesity contributes as much as BP to decreases in LV diastolic function at a community level, that this effect is driven largely by abdominal obesity and is independent of LVH, geometric LV remodelling, and a number of haemodynamic factors, including aortic stiffness and 24-hour BP. The mechanisms of this effect require further elucidation.

CHAPTER 3

Independent Relationship Between Insulin Resistance and an Abnormal Left Ventricular Diastolic Function in a Community Sample with a High Prevalence of Obesity.

.

Abstract

It is uncertain whether relationships between insulin resistance and abnormalities of left ventricular diastolic function represent confounding effects of coexistent obesity or haemodynamic changes. In 478 randomly selected participants from a community sample, the adiposity index-independent relationship between the homeostasis model assesment of insulin resistance (HOMA-IR) and left ventricular early-to-late (E/A) transmitral velocity (echocardiography) was assessed. 43% of the sample were obese. With adjustments for confounders, waist circumference, but not body mass index was independently associated with HOMA-IR. HOMA-IR was inversely correlated with E/A ($p<0.0001$) and in a multivariate model with adjustments for waist circumference, age, sex, conventional diastolic or systolic blood pressure (BP), diabetes mellitus or an HbA1c>6.1%, regular tobacco use, regular alcohol intake, pulse rate, treatment for hypertension and either left ventricular mass index (LVMI) or LV relative wall thickness in the model, the relationship betwreen HOMA-IR and E/A persisted (partial $r=-0.13$ to 0.14, $p<0.005$). With further adjustments for either 24-hour systolic or diastolic BP (partial $r=-0.11$, $p<0.05$, $n=351$) or for aortic pulse wave velocity (partial $r=-0.11$, $p<0.02$, $n=410$), the independent relationship between HOMA-IR and E/A also remained. With HOMA-IR and waist circumference in the same multivariate regression models, HOMA-IR retained an independent relationship with E/A with a magnitude (standardised β-coefficient=0.10±0.03, $p<0.005$) that was equivalent to BP (standardised β-coefficient=0.12±0.04, $p<0.001$), whilst waist circumference failed to show an independent relationship ($p=0.08$). In conclusion, the present results suggest that the relationship between insulin resistance and abnormalities of left ventricular diastolic function may not represent confounding effects of coexistent obesity or haemodynamic alterations. Hence, the relationship between indices of excess adiposity and abnormalities in LV diastolic function may be explained in-part by insulin resistance.

3.0 Introduction

Several studies have demonstrated a relationship between the degree of adiposity and the development of heart failure independent of traditional cardiovascular risk factors (Chen et al 1999, He et al 2001, Johansson et al 2001, Wilhelmsen et al 2001, Kenchaiah et al 2002, 2009, Ingelsson et al 2005a and 2005b, Nicklas et al 2006, Bahrami et al 2008, Spies et al 2009). The transition to heart failure associated with obesity may be mediated by diastolic dysfunction. Indeed, as reviewed in chapters 1 and 2 of the present thesis, excess adiposity is a strong determinant of LV diastolic abnormalities at a community level (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003, Libhaber et al 2009 [analysis in an expanded cohort given in chapter 2], Tsioufis et al 2009, Russo et al 2011). These relationships are independent of a number of confounders including traditional risk factors, LV mass index (LVMI), LV concentric remodelling (as indexed by relative wall thickness), circumferential systolic LV wall stress, 24-hour BP and aortic pulse wave velocity (Libhaber et al 2009 and analysis in an expanded cohort given in chapter 2]). The relationship between obesity and LV diastolic function beyond traditional risk factors and additional haemodynamic and LV structural confounders, begs the question as to the mechanisms that may explain obesity-associated abnormalities in LV diastolic function.

Importantly, insulin resistance, which is often associated with obesity, produces a number of adverse myocardial effects. Insulin resistance may either downregulate myocardial glucose uptake, thus precluding the energetic advantage provided by glucose versus free fatty acid oxidation or result in an accumulation of intracellular triacylglycerol, thus promoting lipotoxicity (Nikolaidis et al 2004, Ouwens et al 2005, Coort et al 2007). These changes may result in impaired myocardial relaxation or increased myocardial stiffness. Thus, one potential explanation for independent relationships between obesity and abnormalities in LV diastolic function is through insulin resistance. However, there is considerable controversy in this regard. Several studies conducted in select clinical samples and with small or relatively small study sizes (Lind et al 1995, Golderisi et al 1997, Mureddu

et al 1998, Watanabe et al 1999, Wong et al 2004, Bajraktari et al 2006, Dinh et al 2010, Utz et al 2011, Sliem et al 2011), or in large study samples (Hwang et al 2011) have suggested that insulin resistance is associated with abnormalities in diastolic function. However, in one study these relationships were not independent of adiposity indices (Mureddu et al 1998) and in other studies (Lind et al 1995, Galderisi et al 1997, Mureddu et al 1998, Watanabe et al 1999, Wong et al 2004, Utz et al 2011, Sliem et al 2011, Hwang et al 2011) these relationships were not adjusted for adiposity indices or indices or central (abdominal) adiposity. This raises the question as to wh ether previously described relationships between insulin resistance and diastolic function may be accounted for by residual confounding central adiposity effects. Moreover, it is uncertain whether these relationships may be accounted for by haemodynamic changes other than clinic blood pressure or heart rate, including 24-hour BP and aortic stiffness. In contrast to studies showing obesity-LV diastolic function relations, in alternative small studies (Olsen et al 2003, Wada et al 2010, Wu et al 2012, Lambert et al 2010) also conducted in select clinical samples, indices of insulin resistance were not correlated with measures of diastolic function.

To address the concerns of a potential selection bias, type I or II statistical errors in small study samples, a lack of adjustment for all appropriate adiposity indices in these prior studies, and the possibility that insulin resistance-diastoic function relationships may be explained by haemodynaimc changes not normally considered (24-hour BP and measures of aortic stiffness), in the present study I evaluated whether an index of insulin resistance is associated with LV diastolic function independent of adiposity indices or haemodynamic changes in a relatively large, randomly selected community-based sample with a high prevalence of obesity.

3.1. Methods

3.1.1 General

A description of the study sample has been provided in chapter 2 (pages 43-44). Of the 678 participants with echocardiographic data fasting blood results were obtained from 478 participants. Demographic and clinical data were obtained using a standardised questionnaire described in chapter 2 (pages 44-45). Height, weight, waist circumference (WC), and sub-scapular and triceps skin-fold thickness (Harpenden callipers) were measured using standard approaches and participants were identified as being overweight if their BMI was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. Central obesity was defined as an enlarged WC (≥88 cm in women and ≥102 cm in men)(Third report of the National Cholesterol Education Program (NCEP) expert panel, 2002). Mean skin-fold thickness was calculated as the mean of sub-scapular and triceps skin-fold thickness values. Standard laboratory blood tests of renal function, liver function, blood glucose (glucose oxidase), lipid profiles, haematological parameters, and percentage glycated haemoglobin (HbA1c)(Roche Diagnostics, Mannheim, Germany) were performed. Fasting plasma insulin concentrations were determined from an insulin immulite, solid phase, two-site chemiluminescent immunometric assay (Diagnostic Products Corporation, Los Angeles, CA, USA) and insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the formula (insulin [uU/ml] x glucose [mmol/l])/22.5 (Wallace et al 2004). Diabetes mellitus (DM) or an abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an HbA1c value greater than 6.1% (Bennett et al 2007). Menopause was confirmed with measurements of follicle stimulating hormone concentrations. Blood pressure (BP) measurements were obtained by a trained nurse-technician using a standard mercury sphygmomanometer and using SpaceLabs monitors (model 90207) (ambulatory 24-hour, day and night BP) as described in chapter 2, page 46..

Carotid-femoral PWV was determined using applanation tonometry and SphygmoCor software as described in chapter 2, pages 46-47.

3.1.2 Echocardiography.

Echocardiography was performed as described in chapter 2, pages 47-55. Left ventricular diastolic function was assessed from a pulsed wave doppler examination of the mitral inflow at rest in all participants with HOMA-IR assessments and myocardial tissue Doppler imaging in 89 participants with HOMA-IR assessments as described in chapter 2, pages 50, 52-53. Left ventricular mass index (LVMI), and LV relative wall thickness were determined as described in chapter 2, page 54. All measurements were recorded and analyzed off-line by experienced investigators whom were unaware of the clinical data of the participants. An LVMI >51 $g/m^{2.7}$ was considered to be increased (Nunez et al 2005).

3.1.3 Data analysis

Database management and statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Continuous data are reported as mean±SD or mean±SEM. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. As HOMA-IR was positively skewed (skewness=3.77, kurtosis=19.2; Shapiro-Wilk's statistic=0.61, p<0.0001) HOMA-IR was log transformed. Log transformation of HOMA-IR resulted in an improved distribution (skewness=0.21, kurtosis=-0.6; Shapiro-Wilk's statistic=0.98). Independent relations between HOMA-IR and diastolic (E/A, e'/a' or E/e') function were determined from multivariate linear regression analysis with adjustments for waist circumference, age, sex, conventional systolic or diastolic BP (or 24-hour BP or PWV), diabetes mellitus or an HbA1c>6.1%, antihypertensive treatment, regular tobacco or alcohol intake, pulse rate and

either LVMI or LV relative wall thickness. Partial correlation coefficients between HOMA-IR and E/A, E/e' or e'/a' were determined by assessing these relations after adjusting for covariates. Probability values were further adjusted for non-independence of family members using the method of maximum likelihood as implemented by the mixed procedure as defined in the SAS package. The mixed model contains both fixed effects (all phenotypic data) parameters and random-effects (familial relationships) parameters. To compare the magnitude of the impact of different variables on E/A, standardized β-coefficients were determined from stepwise linear regression analysis and these coefficients compared using a one way analysis of variance.

3.2 Results

3.2.1 Participant characteristics.

The demographic and clinical characteristics of participants with echocardiographic data either with or without fasting blood data were similar (Table 3.1). A high proportion of participants were overweight or obese (Table 3.1). Of the 42.1% of participants that were hypertensive, only 38.3% had controlled BP. Approximately a quarter of the participants had diabetes mellitus or an impaired blood glucose control. The mean (±SD) HOMA-IR and log HOMA-IR values in those with fasting blood values were 3.70±5.14 and 0.70±1.09 respectively.

The haemodynamic and left ventricular characteristics of the study group are shown in Table 3.2. 23.2% of participants had LVH (LVMI>51 $g/m^{2.7}$). None of the participants had mitral valve abnormalities. Approximately 13% (n=62) had mild diastolic chamber dysfunction or impaired relaxation with an E/A ≤0.75, and ~29% (n=139) severe diastolic chamber dysfunction with an E/A≥1.50.

Table 3.1. General characteristics of study participants with and without fasting blood data.

Fasting blood data	With	Without
Number	478	200
Women (%)	63.8	67.3
Age (years)	43.5±18.0	41.7±17.2
Body mass index (kg/m^2)	29.5±7.8	29.3±7.8
Waist circumference (cm)	90.4±16.2	90.6±17.7
Overweight/obese	24.9/43.1	21.2/43.3
Central obesity	437	47.1
Hypertension	42.1	45.2
Receiving antihypertensives	22.6	22.6
Diabetes mellitus or glycated hemoglobin >6.1%	27.0	21.6
Regular smoking	14.2	15.4
Regular alcohol	22.2	15.9
Conventional systolic BP (mm Hg)	130±22	128±14
Conventional diastolic BP (mm Hg)	84±13	84±14

BP, blood pressure. No significant differences were noted between the groups.

Table 3.2. Haemodynamic and left ventricular parameters in study participants.

		n=
24-Hour systolic BP (mm Hg)	119±15	351
24-Hour diastolic BP (mm Hg	73±10	351
Aortic pulse wave velocity (m/sec)	6.57±2.94	410
LV mass (g)	160±54	478
LV mass indexed for height$^{2.7}$ (g/m$^{2.7}$)	43.814.7	478
LV hypertrophy	23.2	478
E wave velocity (cm/s)	76.3±22.2	478
A wave velocity (cm/s)	65.520.6	478
E/A	1.26±0.48	478
e' wave velocity (cm/sec)	10.74±3.93	89
a' wave velocity (cm/sec)	8.24±3.3	89
e'/a'	1.54±0.84	89
E/a'	6.42±3.58	89
LV ejection fraction (%)	67.0±8.5	478

BP, blood pressure; LV, left ventricular; E, early transmitral velocity; A, late (atrial) transmitral velocity.

3.2.2 Factors related to HOMA-IR.

On bivariate analysis, BMI and waist circumference (Figure 3.1), age (r=0.22, p<0.0001), conventional systolic BP (r=0.12, p<0.01), aortic PWV (r=0.15, p<0.005), central aortic systolic BP (r=0.10, p<0.05), pulse rate (r=0.12, p<0.01), treatment for hypertension (r=0.19, p<0.0001), and diabetes mellitus or an HbA1c>6.1% (r=0.25, p<0.0001) were directly correlated with HOMA-IR. However, in a multivariate regression model, only waist circumference was independently associated with HOMA-IR (Table 3.3). Body mass index was not independently related to HOMA-IR (p=0.25).

3.2.3 HOMA-IR is independently associated with left ventricular mass index and relative wall thicknress

On both bivariate (r=0.22, p<0.0001) and multivariate regression analysis (partial r=0.096, p<0.05), with adjustments for age, waist circumference, sex, regular tobacco use, regular alcohol intake, circumferential systolic stress, treatment for hypertension and diabetes mellitus, HOMA-IR was associated with LVMI. Moreover, on both bivariate (r=0.20, p<0.0001) and multivariate regression analysis (partial r=0.10, p<0.05), with adjustments for age, waist circumference, sex, regular tobacco use, regular alcohol intake, circumferential systolic stress, treatment for hypertension and diabetes mellitus, HOMA-IR was associated with LV relative wall thickness.

3.2.4 Relationship between HOMA-IR and LV diastolic function.

On bivariate analysis, HOMA-IR was strongly and inversely correlated with E/A (Figure 3.2). In a multivariate model with waist circumference, age, sex, conventional diastolic BP, diabetes mellitus or an HbA1c>6.1%, regular tobacco use, regular alcohol intake, pulse rate, and treatment for hypertension in the model, HOMA-IR was independently

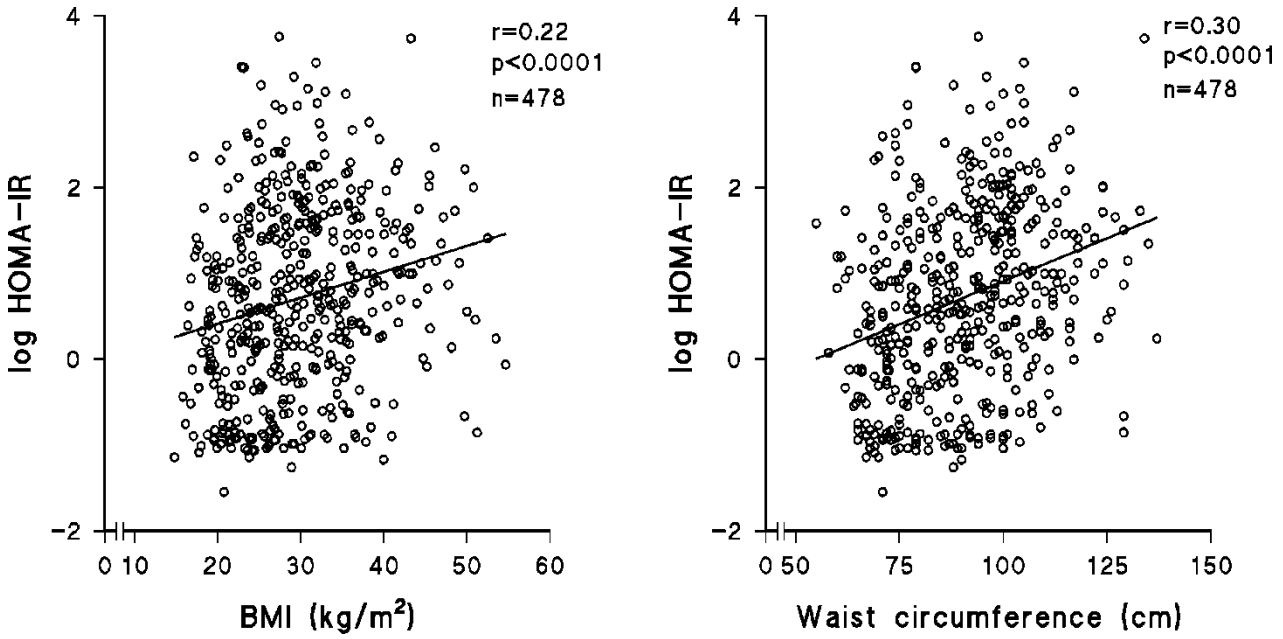


Figure 3.1. Bivariate relationship between indices of excess adiposity and the homeostasis model assesment of insulin resistance (HOMA-IR) in a community sample. BMI, body mass index.

Table 3.3. Factors independently associated with the homeostasis model assessment of insulin resistance (HOMA-IR) in a multivariate regression model .

Variable	Standardized β-coefficient±SEM	p value for relationship
Age	-0.005±0.067	0.94
Waist circumference	0.168±0.058	**<0.005**
Diastolic blood pressure	-0.026±0.056	0.65
Sex	0.049±0.051	0.34
Treatment for hypertension	-0.070±0.052	0.18
Diabetes mellitus or glycated hemoglobin>6.1%	0.115±0.051	**<0.05**
Pulse rate	0.051±0.048	0.29
Regular tobacco	-0.061±0.049	0.21
Regular alcohol	-0.064±0.047	0.17

Bold values are significant. Probability values were further adjusted for non-independence of family members. Significant probability values are indicated in bold. Model r^2=0.13, p<0.0001. Left ventricular mass index was also included in the model.

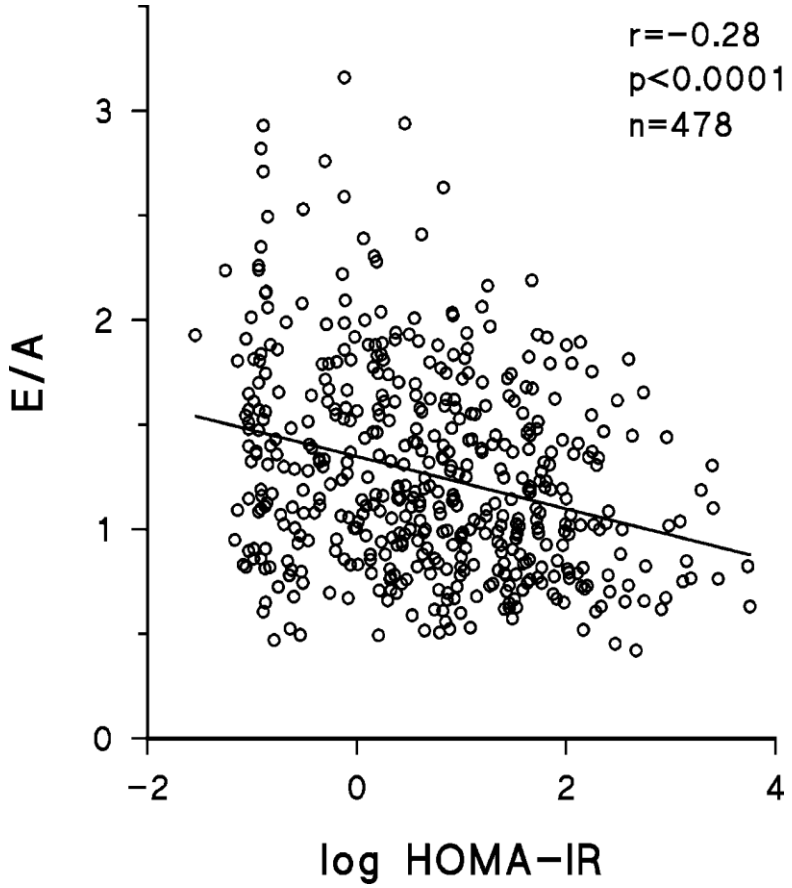


Figure 3.2. Bivariate relationship between the homeostasis model assesment of insulin resistance (HOMA-IR) and left ventricular early-to-late (atrial) transmitral velocity (E/A) in a community sample.

associated with E/A (Figure 3.3). With further adjustments for LVMI or LV relative wall thickness, HOMA-IR retained independent relationships with E/A (Figure 3.3). Moreover, with adjustments for 24-hour systolic or diastolic BP or aortic PWV in place of conventional BP in the multivariate models, HOMA-IR remained independently related to E/A (Figure 3.3).

In the 89 participants with myocardial tissue Doppler assessments, HOMA-IR was correlated with e'/a' ($r=0.29$, $p<0.0001$), but not with E/e' ($r=0.03$, $p=0.78$). However, in a multivariate model with waist circumference, age, sex, conventional diastolic BP, diabetes mellitus or an HbA1c>6.1%, regular tobacco use, regular alcohol intake, pulse rate, and treatment for hypertension in the model, the relationship between HOMA-IR and e'/a' was not retained (partial $r=-0.14$, $p=0.18$).

3.2.5 Comparison of the quantitative impact of HOMA-IR versus alternative factors on LV diastolic function

Table 3.4 shows a comparison of the standardized β-coefficients (slopes) for the independent relations between variables associated with E/A in multivariate regression models. The relations between HOMA-IR and E/A were similar irrespective of whether LVMI was (Table 3.4) or was not (standardized β-coefficient=-0.105±0.034, $p<0.005$) included in the regression model. Similar outcomes were noted with systolic as opposed to diastolic BP in the regression model (HOMA-IR versus E/A adjusted for confounders and systolic BP: standardized β-coefficient=-0.099±0.034, $p<0.005$). The magnitude of the effect of HOMA-IR on E/A was comparable with the effect of BP on E/A and second only to the magnitude of the effect of age on E/A (comparison of the standardized β-coefficients inTable 3.4). With both HOMA-IR and waist circumference included in a multivariate model, although the relationship between HOMA-IR and E/A persisted, the relationship between waist circumference and E/A no longer achieved significance (Table 3.4).

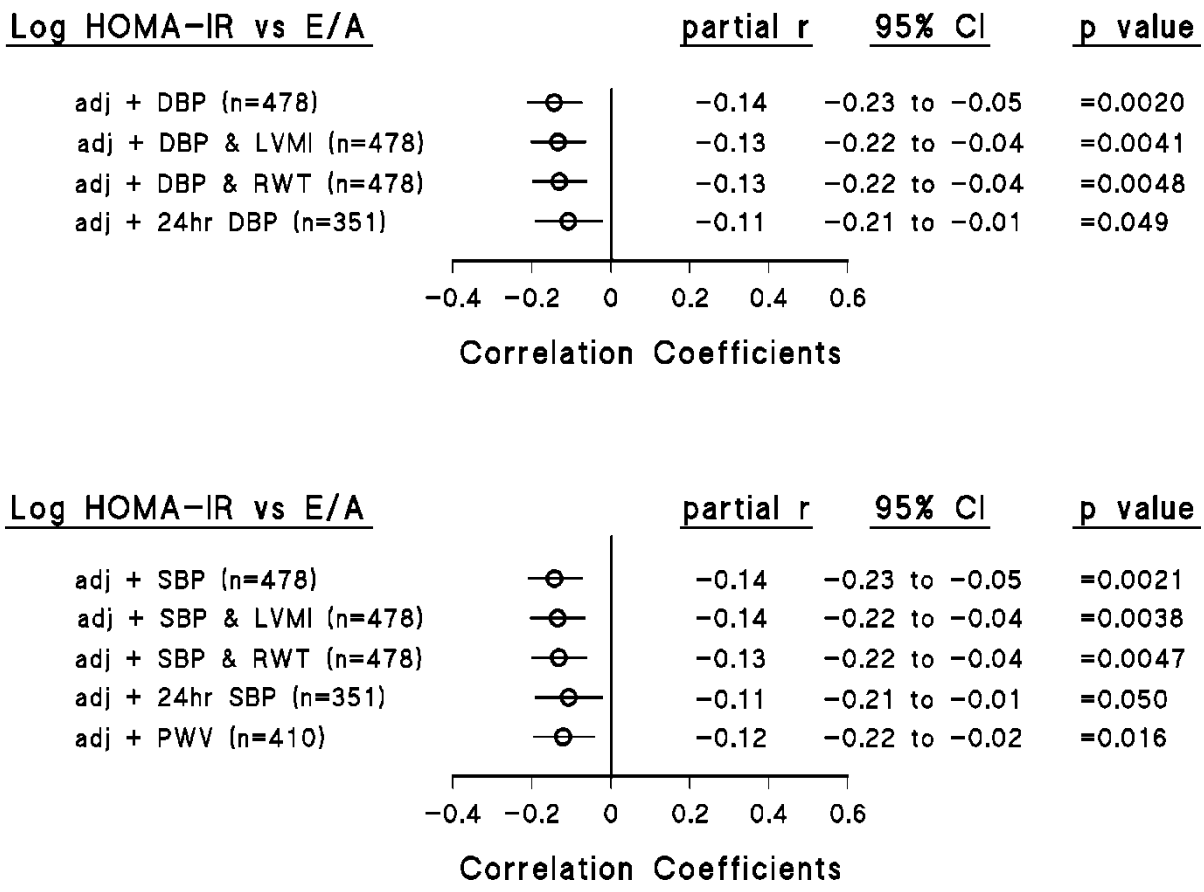


Figure 3.3. Multivariate adjusted (adj) relationships (partial correlation coefficients [partial r] and 95% confidence intervals [CI]) between the homeostasis model assesment of insulin resistance (HOMA-IR) and left ventricular early-to-late (atrial) transmitral velocity (E/A) in a community sample. DBP, diastolic blood pressure; SBP, systolic BP; LVMI, left ventricular mass index; RWT, LV relative wall thickness; PWV, aortic pulse wave velocity. Adjustments are for waist circumference, age, sex, conventional BP (or 24-hour BP, or PWV as indicated), diabetes mellitus or an HbA1c>6.1%, regular tobacco use, regular alcohol intake, pulse rate, treatment for hypertension, and LVMI or RWT as indicated in the models.

Table 3.4.. Comparison of the impact of factors associated with left ventricular E/A in a multivariate regression model in the study group (n=478).

Variable	Standardized β-coefficient±SEM	p value for relationship
Age	-0.542±0.045	**<0.0001**
Waist circumference	-0.076±0.043	=0.075
HOMA-IR	-0.098±0.034	**<0.005**
Diastolic blood pressure	-0.121±0.035	**<0.001**
Sex	0.059±0.037	=0.11
Treatment for hypertension	0.021±0.038	=0.57
Diabetes mellitus or glycated hemoglobin>6.1%	-0.033±0.37	=0.37
Left ventricular mass index	-0.064±0.036	=0.079
Pulse rate	-0.071±0.035	**<0.05**
Regular tobacco	0.045±0.036	=0.20
Regular alcohol	0.027±0.034	=0.43

HOMA-IR, homeostasis model assesment of insulin resistance. Probability values were further adjusted for non-independence of family members. Significant probability values are indicated in bold. Model r^2=0.54, p<0.0001. No significant differences were noted between β-coefficients for HOMA-IR and diastolic blood pressure.

3.3 Discussion

The main findings of the present study are that in a randomly selected community sample with a high prevalence of obesity, insulin resistance, as indexed by HOMA-IR was associated with E/A independent of a number of confounders as well as waist circumference, the main adiposity index that explains variations in E/A. Importantly, these independent relations were also beyond structural LV changes, including LVMI and relative wall thickness as well as 24-hour BP and aortic PWV.

To the best of my knowledge the present study is the first to provide strong evidence to show that insulin resistance is associated with an abnormal LV diastolic function independent of appropriate adiposity indices. In this regard, these findings are consistent with the results of several small studies which are nevertheless subject to false positive findings and a selection bias (Lind et al 1995, Golderisi et al 1997, Mureddu et al 1998, Watanabe et al 1999, Wong et al 2004, Bajraktari et al 2006, Dinh et al 2010, Utz et al 2011, Sliem et al 2010), and one large study, which was nevertheless also conducted in a select clinical sample (Hwang et al 2011). Importantly, in one small study reporting on obesity-LV diastolic function relations, these relationships were not independent of adiposity indices (Mureddu et al 1998) and in other studies (Lind et al 1995, Golderisi et al 1997, Mureddu et al 1998, Watanabe et al 1999, Wong et al 2004, Dinh et al 2010, Utz et al 2011, Sliem et al 2010, Hwang et al 2011) these relationships were either not adjusted for adiposity indices or were adjusted for BMI rather than indices or central (abdominal) adiposity. With respect to adjustments for indices of central adiposity, as indicated in the present study, waist circumference, but not BMI was independently associated with HOMA-IR. Thus, previously reported associations between insulin resistance and LV diastolic function may not only be attributed to either false positive results, or a selection bias, but also to confounding effects of central obesity *per se*.

In contrast to the present and prior studies (Lind et al 1995, Golderisi et al 1997, Mureddu et al 1998, Watanabe et al 1999, Wong et al 2004, Bajraktari et al 2006, Utz et al

2011, Sliem et al 2010, Hwang et al 2011) showing relations between obesity and LV diastolic function, in alternative small studies (Olsen et al 2003, Wada et al 2010, Wu et al 2011, Lambert et al 2010), indices of insulin resistance were not correlated with measures of diastolic function. However, the small sample sizes may have resulted in false negative findings and a selection bias may have resulted in recruitment of participants that do not reflect the community at large.

Importantly, in the present study I noted a modest independent relationship between HOMA-IR and LVMI or relative wall thickness. As LV diastolic function is strongly determined by LVMI and relative wall thickness (Schillaci et al 2002, Fischer et al 2003, Chahal et al 2010), I thus assessed the relationship between HOMA-IR and LV diastolic function with adjustments for LVMI or relative wall thickness. In this regard, adjustments for either LVMI or relative wall thickness failed to modify the multivariate adjusted HOMA-IR-E/A relationships. These data would therefore suggest that LV structural changes are unlikely to account for relationships between HOMA-IR and LV diastolic function.

With respect to the clinical implications of the present findings, as discussed in chapter 2 of the present thesis, obesity effects on LV diastolic function may represent a progressive preclinical condition that contributes to obesity-induced heart failure (Chen et al 1999, He et al 2001, Johansson et al 2001, Wilhelmsen et al 2001, Kenchaiah et al 2002, 2009, Ingelsson et al 2005a and 2005b, Nicklas et al 2006, Bahrami et al 2008, Spies et al 2009). In this regard, as suggested by the present study, insulin resistance may mediate this effect and hence may represent a potential target to prevent the transition to heart failure in obesity. The present findings suggest that the relationship between insulin resistance and heart failure (Ingelsson[a] et al 2005) may be in-part accounted for by the adverse effects of insulin resistance on LV diastolic function.

The present study has several strengths and limitations. The strengths of the study include the use of ambulatory BP and arterial stiffness assessments to adjust for the impact of haemodynamic factors on the relationships between HOMA-IR and diastolic function in a cohort of participants. Thus, the chances of the independent relationship noted between

HOMA-IR and E/A being attributed to inappropriate estimates of BP or haemodynamic factors being employed are likely to have been reduced. Second, I evaluated relations between HOMA-IR and E/A using BP and E/A as continuous rather than dichotomous traits, thus improving the probability of a positive outcome.

The limitations of the study are first the cross-sectional rather than prospective nature of the study design and hence relationships between HOMA-IR and E/A may not be causal. Second, I did not measure pulmonary venous reverse flow and mitral inflow during the peak of the valsalva maneuver, and hence I may have missed some participants with diastolic dysfunction. Moreover, tissue Doppler assessments were available in only a small cohort of the total sample. I may thus have missed participants with pseudonormal filling patters. Thus, I did not assess the relationship between HOMA-IR and the presence of diastolic dysfunction reported as a discrete trait. Third, the limited proportion of male participants recruited for the study prevented sex-specific analyses, and thus the effect reported on in the present study may be restricted to females. Fourth, LV ejection fraction was measured with echocardiography whilst magnetic resonance imaging (MRI) measurements of systolic function have been demonstrated to be more sensitive for predicting cardiovascular events (Mewton et al 2013). Fifth, the relationships between HOMA-IR and E/A after adjustments for 24 hour BP, or aortic wave velocity only achieved a trend for significance ($p<0.05$) and hence a larger sample size is required to confirm these data. Importantly however, even with waist circumference in the same model, HOMA-IR achieved quantitatively the third greatest effect on E/A next to age and diastolic BP. Last, relatively weak partial r values were noted for relationships between HOMA-IR and E/A, a finding that must be interpreted with caution. This may reflect an overall weak relationship between insulin resistance and E/A; an inability to appropriately account for all confounders or to exclude the impact of co-linearity between adjustors in multivariate models; or to an inability to accurately assess the degree of insulin resistance using for example a euglycaemic insulin clamp. Only intervention studies are likely to reveal the actual magnitude of the effect of insulin resistance on E/A if indeed this relationship is cause and effect.

In conclusion, the results of the present study suggest that with adjustments for appropriate adiposity indices (waist circumference) and other confounders, HOMA-IR contributes as much as BP to decreases in LV diastolic function at a community level, and that this effect is independent of LVH, geometric LV remodelling, and a number of haemodynamic factors, including aortic stiffness and 24-hour BP. The mechanisms of this effect require further elucidation. These data lend insights into the potential for the development of therapeutic strategies targeting insulin resistance to prevent the transition to heart failure in obesity.

CHAPTER 4

Relationship Between Inappropriate Left Ventricular Hypertrophy and Ejection Fraction Independent of Absolute or Indexed Mass in a Community Sample With a High Prevalence of Obesity.

Published in-part as: Libhaber CD, Norton GR, Maseko MJ, Majane OHI, Millen AME, Maunganidze F, Michel FS, Brooksbank R, Libhaber E, Sareli P, Woodiwiss AJ. Relationship between inappropriate left ventricular hypertrophy and ejection fraction independent of absolute or indexed mass in a community sample of black African ancestry. J Hypertens. 2013;31(1):169-76

Abstract

It is unclear whether left ventricular hypertrophy (LVH) which exceeds that predicted from workload (inappropriate LV mass [LVM_{inappr}]), is associated with reduced LV systolic chamber function independent of and more closely than absolute or indexed LVM. It is also uncertain to what extent obesity contributes toward variations in LVM_{inappr} at a community level. In 626 randomly selected adult participants from a community sample with a high prevalence of obesity, using echocardiography I assessed absolute LVM, LVM indexed to $height^{2.7}$ (LVMI), LVM_{inappr}, LV wall stress, ejection fraction (EF), and midwall fractional shortening (FSmid). LVM_{inappr} was determined as % observed/predicted LVM. Predicted LVM was calculated from a previously validated formula that incorporates stroke work. $LVMI_{inappr}$>150% was considered to be inappropriate LVH. This threshold was identified from the upper 95% confidence interval for $LVMI_{inappr}$ determined in 140 healthy participants. 21.7% of participants had LVH (LVMI>51g/$m^{2.7}$) and 18.5% had inappropriate LVH. The strongest independent predictor of inappropriate LVH was body mass index (BMI)($p<0.0001$). With adjustments for LV stress and other confounders there was a strong inverse relationship between LVM_{inappr} and EF (partial $r=-0.41$, $p<0.0001$), whilst only modest inverse relations between LVM or LVMI and EF were noted (partial $r=-0.07$ to -0.09, $p<0.05$-0.09)($p<0.0001$, comparison of partial r values). The independent relationship between LVM_{inappr} and EF persisted with further adjustments for LVM or LVMI (partial $r=-0.52$, $p<0.0001$). LVM_{inappr} and FSmid were similarly inversely related ($p<0.0001$) and these relations were also stronger than and independent of LVM or LVMI. In conclusion, in a community sample with a high prevalence of obesity, inappropriate LVH is strongly and inversely related to variations in EF independent of and more closely than LVM or LVMI and BMI was the strongest independent determinant of inappropriate LVH. These data suggest that LVH is a compensatory response to workload, but when exceeding that predicted by workload, as may occur in obesity, is associated with LV systolic chamber decompensation.

4.0 Introduction

The independent relationship between excess adiposity and LV systolic chamber function is controversial, with some studies showing a relationship (Ammar et al 2008, Chinali et al 2006, Scaglione et al 1992, Karason et al 1998, Alpert et al 1995), whilst the majority of studies have failed to do so (Pascual et al 2003, de Devitiis et al 1981, Zarich et al 1991, Stoddard et al 1992, De Simone[b] et al 1996, Mureddu et al 1996, Iacobellis et al 2002, Peterson et al 2004, Wong et al 2004, Turkbey et al 2010, Powell et al 2006, Bazzano et al 2011, Russo et al 2011). One possible explanation for these discrepancies is that the transition to LV systolic chamber dysfunction in obesity depends on the extent of left ventricular hypetrophy (LVH).

Left ventricular hypertrophy is indeed an independent predictor of a reduced LV ejection fraction (EF) (Drazner et al 2004). However, an increased LV mass (LVM) (Aurigemma et al 1995, de Simone et al 1994[b], Shimizu et al 1991) or on-treatment decreases in LVM (Perlini et al 2001) have also been associated with an unchanged EF. In addition, LVH may even be associated with an enhanced EF for that predicted by wall stress (Hartford et al 1985) and on-treatment decreases in LVM have been related to an attenuation of rather than enhancement of indices of LV systolic chamber function (Wachtell et al 2002). One explanation for the variable relationships between LVM or LVM index (LVMI) and LV systolic chamber function (Aurigemma et al 1995, de Simone[b] et al 1994, Shimizu et al 1991, Perlini et al 2001, Hartford et al 1985, Wachtell et al 2002) is that LVH in-keeping with work load (i.e. stroke work=blood pressure x stroke volume) is compensatory, whilst that exceeding workload (i.e. “inappropriate” LVM [LVM_{inappr}]) (de Simone et al 1998) contributes toward decompensation. Indeed a number of studies have demonstrated an inverse relationship between LVM_{inappr} and LV systolic chamber 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). As obesity has been demonstrated in some studies conducted in select samples, to be related to LVM_{inappr} (Palmieri et al 1999, Palmieri et al 2001,

Calentano et al 2001, Palmieri et al 2004, de Simone et al 2004, Chinali et al 2006, Lopez et al 2007, Chinali et al 2007, Ratto et al 2008) it is possible that obesity-induced LVM_{inappr} may translate into LV systolic chamber dysfunction. However, there are a number of unresolved issues with respect to the role of LVM_{inappr} as a determinant of EF and the role of obesity as a mediator of LVM_{inappr}.

With regards to the unresolved issue of the role of LVM_{inappr} as a determinant of EF, some prior studies conducted in select clinical samples have demonstrated inverse correlations between LV systolic chamber function and both absolute LVM as well as LVM_{inappr} (Palmieri et al 1999, Palmieri et al 2001) and in one of these studies LVM was equally as strongly inversely correlated with EF as LVM_{inappr} (Palmieri et al 2001). This finding is at odds with the notion that it is only LVM beyond stroke work that explains decompensation. Thus, further studies are required in non-selected samples to evaluate whether LVM_{inappr} is inversely associated with LV systolic chamber function independent of LVM or LVMI.

With respect to the unresolved issue of the role of obesity as a possible determinant of LVM_{inappr} although the aforementioned studies (Palmieri et al 1999, Palmieri et al 2001, Calentano et al 2001, Palmieri et al 2004, de Simone et al 2004, Chinali et al 2006, Lopez et al 2007, Chinali et al 2007, Ratto et al 2008), have demonstrated this relationship, these associations were not adjusted for confounders and in other select study samples (de Simone et al 2001, Mureddu et al 2001, Muiesan et al 2007, Cioffi et al 2011) obesity was not related to LVM_{inappr} even in unadjusted models. Moreover, whether relationships between obesity and LVM_{inappr} can be accounted for by increases in alternative haemodynamic factors such as an increased 24-hour BP, aortic PWV and changes in circumferential wall stress is uncertain. Indeed, in one study both BMI and 24-hour BP were increased in 16 hypertensives with inappropriate LVH as compared to 164 hypertensives with an appropriate LVM (Palmieri et al 1999). Therefore, the extent to which obesity contributes toward LVM_{inappr} at a community level independent of confounders and additional haemodynamic

factors and whether LVM_{inappr} is associated with a reduced systolic chamber function independent of and more strongly than absolute or indexed LVM, is uncertain.

As the extent of the contribution of obesity toward LVM_{inappr} and whether inverse relationships between LVM_{inappr} and EF are independent of absolute LVM are unclear, in the present study conducted in a randomly selected community sample of black African ancestry with a high prevalence of obesity, I therefore aimed to evaluate i) whether LVM_{inappr} is inversely associated with EF independent of and more strongly than LVM or LVMI and ii) the extent to which obesity contributes toward variations in LVM_{inappr} independent of all confounders and 24-hour BP and aortic PWV.

4.1 Methods

4.1.1 General

A description of the study sample has been provided in chapter 2 (pages 43-44). Demographic and clinical data were obtained using a standardised questionnaire described in chapter 2 (pages 44-45). Height and weight were measured using standard approaches and participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. Standard laboratory blood tests of renal function, liver function, blood glucose, lipid profiles, haematological parameters, and percentage glycated haemoglobin (HbA1c)(Roche Diagnostics, Mannheim, Germany) were performed. Diabetes mellitus (DM) or an abnormal blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an HbA1c value greater than 6.1% (Bennett et al 2007). Menopause was confirmed with measurements of follicle stimulating hormone concentrations. Blood pressure (BP) measurements were obtained by a trained nurse-technician using a standard mercury sphygmomanometer and using SpaceLabs monitors (model 90207) (ambulatory 24-hour, day and night BP) as described in chapter 2, page 46.

Carotid-femoral PWV was determined using applanation tonometry and SphygmoCor software as described in chapter 2, pages 46-47.

4.1.2 Echocardiography.

Echocardiography was performed as described in chapter 2, pages 47-55. All measurements were recorded and analyzed off-line by experienced investigators who were unaware of the clinical data of the participants. Left ventricular mass (LVM), LVMI, and LV mean wall thickness were calculated as described in chapter 2, page 54. LVMI >51 $g/m^{2.7}$ was considered to be increased (Nunez et al 2005). Left ventricular ejection fraction (EF) and midwall fractional shortening (FSmid) were calculated to determine LV pump and myocardial systolic function respectively. The assessment of EF is as described in chapter 2, page 54. An EF of <55% was considered to be a reduced EF. A threshold of 55% was supported by identifying the lower 5% confidence interval for EF (55.8%) in 140 participants from the community-based study without clinically significant disease and normal clinical blood parameters who were normotensive, non-diabetic, and had a BMI<30 kg/m^2. Midwall fractional shortening (FSmid) was calculated using a previously described formula (de Simone[b] et al 1996) as [(LVIDed + 0.5 Hed)-(LVIDes + 0.5 Hes)]/(LVIDed + 0.5 Hed), where LVID is left ventricular internal diameter, H is wall thickness, ed is end diastole and es is end systole. The calcution of FSmid using a modified ellipsoidal model and as previously described (de Simone[b] et al 1996) accounts for epicardial migration of the midwall during systole. Stroke volume was evaluated from the difference between LV end diastolic and systolic volumes determined using both the Teichholz (Teichholz et al 1976) and the Z-derived (de Simone[c] et al 1996) methods. Circumferential LV systolic wall stress was calculated as previously described (Shimizu et al 1991) as:

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

where SBP is systolic blood pressure, LVIDs is LVID in systole and PWTs is posterior wall thickness in systole.

The extent of inappropriate LVM (LVM_{inappr}) was determined from predicted LVM as described by others (de Simone et al 2002), where predicted LVM was calculated as $55.37+(6.64 \times height^{2.7})+(0.64 \times [systolic\ BP \times stroke\ volume \times 0.014]) - (18.07 \times gender)$, where male gender=1 and female gender=2, and where stroke volume was calculated from LV volumes assessed from the Z-derived method. Inappropriate LVM was expressed either as actual-predicted LVM in grams, or % actual LVM/predicted LVM. An $LVMI_{inappr}$>150% was considered to be increased. This threshold was identified from the upper 95% confidence interval for $LVMI_{inappr}$ determined in the same 140 participants employed to define thresholds for EF. In these participants the upper 95% confidence for LVMI was 51.8 $g/m^{2.7}$. To ensure that the calculation for LVM_{inappr} was suitable for the community studied, I determined whether the strong correlations between LVM or LVMI and stroke work were eliminated if LVM was expressed as LVM_{inappr}.

4.1.3 Data analysis

Database management and statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Continuous data are reported as mean±SD or mean±SEM. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. Independent relations between LVM, LVMI or LVM_{inappr} and LV function were assessed from multivariate linear regression analysis with appropriate adjustors. Z-Statistics were used to compare correlation coefficients. Probability values were further adjusted for non-independence of family members using the method of maximum likelihood as implemented by the mixed procedure as defined in the SAS package.

4.2 Results

4.2.1 Participant characteristics.

The demographic and clinical characteristics of those with and without echocardiographic data were similar (Table 4.1). A high proportion of participants were obese (Table 4.1). Of the 43% of participants that were hypertensive, only 36% had controlled BP. 18.5% of participants had inappropriate increases in LVM ($LVMI_{inappr}$>150%). 21.7% of participants had LVH (LVMI>51 $g/m^{2.7}$). In the treated hypertensives 85.7% of participants were receiving low dose hydrochlorothiazide, 15.7% calcium channel blockers, 21.1% angiotensin-converting enzyme inhibitors (ACEI) and 2.0% beta adrenergic receptor blockers (β-blockers). None of the participants were receiving angiotensin receptor antagonists (ARB) or aldosterone receptor antagonists.

4.2.2 Suitability of the LVM_{inappr} calculation.

In contrast to strong positive correlations noted between LVM (or LVMI) and stroke work (r=0.60-0.67, p<0.0001), when LVM was expressed as LVM_{inappr}, relations with stroke work were eliminated (r=-0.02, p=0.67).

4.2.3 Clinical and demographic factors associated with an increased LVM_{inappr} or LVMI.

Participants with an increased LVM_{inappr} or LVMI were older; consisted of more women; had a greater BMI and waist circumference; had more diabetes mellitus or an uncontrolled blood glucose; and more were receiving antihypertensive therapy (Table 4.2). Participants with an increased LVM_{inappr} also had a higher pulse rate, but fewer smoked and consumed alcohol regularly (Table 4.2). Participants with an increased LVMI, but not those with an increased LVM_{inappr} had an increased conventional (Table 4.2), and 24 hour, day and

Table 4.1. Characteristics of study participants with and without echocardiographic data.

Echocardiography	With	Without
Number (% women)	626 (65.0)	565 (65.5)
Age (years)	43±18	44±19
Body mass index (kg/m^2)	29.3±7.6	29.6±8.5
Waist circumference (cm)	90.3±16.6	90.2±16.8
% Overweight/obese	23.8/42.5	22.1/43.0
% Hypertension	43.0	41.6
% Receiving antihypertensives	23.5	23.0
% Treated for diabetes mellitus	8.0	5.5
% Diabetes mellitus or HbA1c >6.1%	27.0	23.4
% Regular smoking	14.1	15.9
% Regular alcohol	20.1	22.3
Conventional systolic BP/ diastolic BP (mm Hg)	129±22/84±13	130±23/85±13

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

Table 4.2. Characteristics of participants with or without increases in left ventricular mass (LVM) indexed to height$^{2.7}$ (LVMI) or inappropriate increases in LVM (LVM_{inappr}).

	LVM_{inappr}		LVMI	
	>150%	≤150%	>51 g/m$^{2.7}$	≤51 g/m$^{2.7}$
Sample size (% female)	116 (83.6)***	510 (60.8)	136 (68.4)	490 (64.1)
Age (years)	49.2±7.1***	41.5±17.8	54.4±15.7***	28.1±7.2
Body mass index (kg/m^2)	34.6±7.1***	28.2±7.3	33.9±7.6***	28.1±7.2
Waist circumference (cm)	101±16***	88±16	99±17***	88±16
% DM or HbA1c>6.1%	41.4**	23.7	42.7***	22.7
% Treated for hypertension	36.2**	20.6	42.7***	18.2
Regular smoking (%)	5.2**	16.1	9.6	15.3
Regular alcohol (%)	12.1*	22.0	20.6	20.0
Conventional SBP (mm Hg)	128±20	129±23	141±24***	126±21
Conventional DBP (mm Hg)	83±11	84±13	89±13***	83±12
Pulse rate (beats/min)	69±14**	64±12	66±14	65±12
LV systolic wall stress (g/cm^2)	111±29	113±29	116±32	112±29

All continuous data are expressed as mean±SD. DM, diabetes mellitus; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic BP; LV, left ventricle. *p<0.05, ** p<0.001, ***p<0.0001 vs LVM_{inappr} ≤150% or LVMI≤51 g/m$^{2.7}$.

night BP (data not shown). However, LV systolic wall stress was similar between the groups (Table 4.2).

4.2.4 Relationships between indices of excess adiposity and LVM_{inappr}.

In bivariate analysis, indices of adiposity were strongly associated with LVM_{inappr} (Figure 4.1). In a multivariate model with adjustments for confounders, indices of adiposity were strongly and independently associated with LVM_{inappr} irrespective of whether conventional BP (Table 4.3), circumferential wall stress (Table 4.4), aortic PWV (Table 4.4), or 24 hour BP (Table 4.4) were included in the multivariate model.

4.2.5 Left ventricular structure and systolic function in participants with an increased LVM_{inappr} or LVMI.

Participants with an increased LVMI and LVM_{inappr} had an increased LVM, LVMI, LV mean wall thickness and LV end diastolic diameter as compared to participants with a normal LVMI and LVM_{inappr} (Table 4.5). Either with adjustments for confounders or unadjusted, LV EF and FSmid were decreased in participants with an increased LVM_{inappr} (Table 4.5). In contrast, both LV EF and FSmid were similar in participants with as opposed to without an increased LVMI (Table 4.5). Secondary data analysis with adjustments for the use of ACEIs or β-blockers in place of “treatment for hypertension” produced essentially the same differences in LVEF and FSmid between the groups (Table 4.6).

4.2.6 Relationship between LVM, LVMI, or LVM_{inappr} and EF or FSmid.

On bivariate and multivariate regression analysis with LV systolic wall stress and other confounders included as adjustors; LVM_{inappr} was strongly and inversely associated with EF and FSmid (Figure 4.2 and Table 4.7). In contrast, LVM and LVMI showed only a

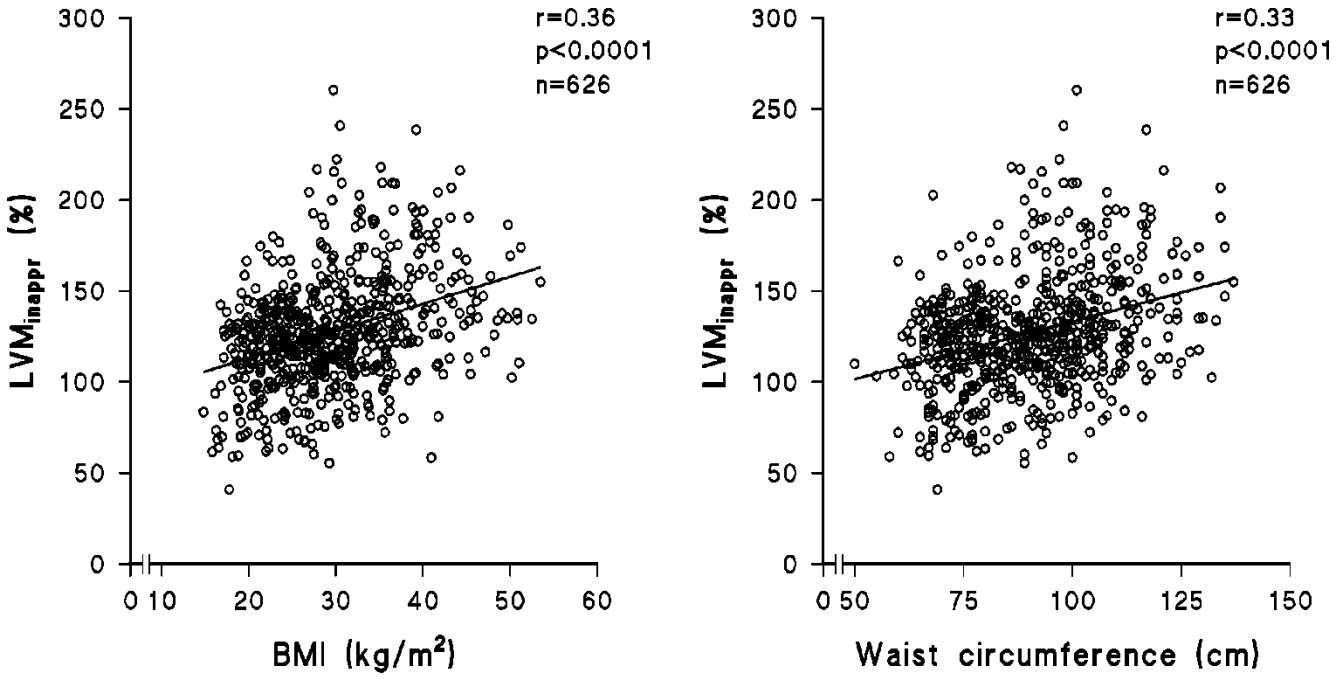


Figure 4.1. Bivariate relationships between indices of adiposity and left ventricular mass (LVM) that exceeds that predicted from LV workload (inappropriate LVM [$LVM_{inappr.}$])

Table 4.3. Independent relationships between indices of excess adiposity and left ventricular mass (LVM) beyond that predicted by stroke work (inappropriate LVM [LVM_{inappr}]) in 626 participants of a community sample.

LVM_{inappr} vs	Standardised β-coefficient±SEM	p value
	Model with waist circumference	
Age	-0.048±0.05	=0.54
Female sex	0.141±0.042	**=0.0007**
Waist circumference	0.267±0.047	**<0.0001**
DM and/or HbA1c>6.1%	0.068±0.042	=0.09
Pulse rate	0.022±0.038	=0.21
Treatment for hypertension	0.029±0.045	=0.27
Smoking	-0.041±0.042	=0.58
Alcohol	-0.011±0.039	=0.67
	Model with body mass index	
Age	-0.026±0.048	=0.82
Female sex	0.087±0.044	**<0.05**
Body mass index	0.280±0.047	**<0.0001**
DM and/or HbA1c>6.1%	0.076±0.041	=0.06
Pulse rate	0.036±0.038	=0.12
Treatment for hypertension	0.025±0.045	=0.30
Smoking	-0.042±0.042	=0.55
Alcohol	-0.007±0.039	=0.74

DM, diabetes mellitus. Also included in the models was systolic blood pressure. Probability values are further adjusted for non-independence of family members.

Table 4.4. Relationships between indices of excess adiposity and left ventricular mass (LVM) beyond that predicted by stroke work (inappropriate LVM [LVM_{inappr}]) with adjustments for potential confounders and haemodynamic factors as indicated.

LVM_{inappr} vs	n=	Adustments	Partial r	CI	p value
Waist circumference	626	* + SBP	0.24	0.164 to 0.312	<0.0001
	626	* + LV wall stress	0.23	0.157 to 0.306	<0.0001
	559	* + aortic PWV	0.23	0.148 to 0.307	<0.0001
	437	* + 24-hour SBP	0.23	0.157 to 0.306	<0.0001
Body mass index	626	* + SBP	0.26	0.182 to 0.330	<0.0001
	626	* + LV wall stress	0.24	0.167 to 0.316	<0.0001
	559	* + aortic PWV	0.25	0.167 to 0.323	<0.0001
	437	* + 24-hour SBP	0.26	0.169 to 0.345	<0.0001

CI, confidence intervals; SBP, systolic blood pressure; PWV, pulse wave velocity. *Adustments are for age, sex, pulse rate, treatment for hypertension, diabetes mellitus oand/or HbA1c>6.1%, regular alcohol intake, regular smoking. Probability values are further adjusted for non-independence of family members.

Table 4.5. Left ventricular (LV) structural characteristics and systolic function in participants with or without increases in left ventricular mass (LVM) indexed to height$^{2.7}$ (LVMI) or inappropriate increases in LVM (LVM_{inappr}).

	LVM_{inappr}		LVMI	
	>150%	≤150%	>51 g/m$^{2.7}$	≤51 g/m$^{2.7}$
Sample size	116	510	136	490
LVM (g)	202±54***	145±43	218±44***	138±36
LVM indexed for height$^{2.7}$ (g/m$^{2.7}$)	57.4±16.6***	39.4±11.2	62.6±12.5***	37.3±8.7
% Actual LVM/Predicted LVM	176±22***	116±21	156±33***	119±26
Actual LVM-predicted LVM (g)	87±33***	20±27	74±40***	21±28
LV mean wall thickness (cm)	1.04±0.24***	0.86±17	1.06±0.20***	0.84±0.17
LV end diastolic diameter (cm)	4.91±0.61**	4.72±0.55	5.18±0.53***	4.63±0.52
LV ejection fraction (%)	63.2±10.0***	67.7±8.2	66.6±9.9	67.0±8.4
Adjusted† LV ejection fraction (%)	62.3±7.8***	67.9±7.5	66.5±8.1	67.0±7.8
LV FSmid (%)	20.9±5.6***	23.5±5.2	22.7±5.9	23.1±5.2
Adjusted† LV FSmid (%)	20.9±5.5***	23.5±5.2	23.1±5.6	23.0±5.3

FSmid, midwall fractional shortening. *p<0.05, ** p<0.001, ***p<0.0001 vs LVM_{inappr} ≤150% or LVMI≤51 g/m$^{2.7}$.†Multivariate adjustments are for age, sex, LV circumferential systolic wall stress, HbA1c, pulse rate, treatment for hypertension, regular smoking, regular alcohol intake, and waist circumference. Probability values are further adjusted for non-independence of family members.

Table 4.6. Multivariate adjusted (including adjustments for the use of angiotensin-converting enzyme inhibitors [ACEI] and beta adrenergic receptor blockers [β-blockers]) left ventricular (LV) systolic function in participants with or without increases in left ventricular mass (LVM) indexed to height$^{2.7}$ (LVMI) or inappropriate increases in LVM (LVM_{inappr}).

	LVM_{inappr}		LVMI	
	>150%	≤150%	>51 g/m$^{2.7}$	≤51 g/m$^{2.7}$
Sample size	116	510	136	490
Adjusted† LV ejection fraction (%)	62.4±7.8	67.9±7.5*	66.5±8.1	67.0±7.8
Adjusted† LV FSmid (%)	20.9±5.4	23.5±5.2*	23.1±5.6	23.0±5.3

FSmid, midwall fractional shortening. *p<0.0001 vs LVM_{inappr} ≤150% or LVMI≤51 g/m$^{2.7}$.†Multivariate adjustments are for age, sex, LV systolic stress, HbA1c, pulse rate, the use of ACEIs and β-blockers, regular smoking, regular alcohol intake, waist circumference. Probability values are further adjusted for non-independence of family members.

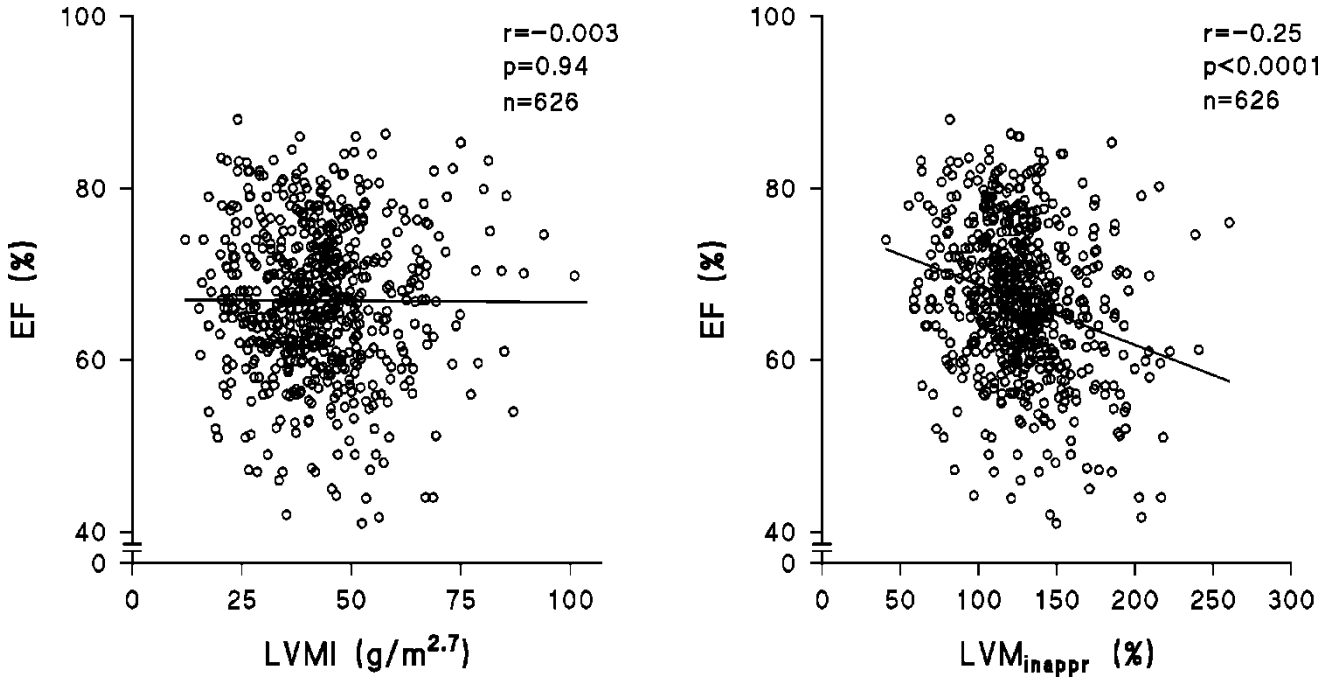


Figure 4.2. Bivariate relationships between left ventricular mass index (LVMI) or inappropriate LVM (LVM_{inappr}) and LV ejection fraction (EF).

Table 4.7. Relationships between indexes of left ventricular mass (LVM) and systolic function with LVM expressed as an inappropriate increase in LVM (LVM_{inappr}), absolute LVM or LVM indexed to height$^{2.7}$ (LVMI)(n=626).

	Pearson's r (CI)	p value	Partial r (CI)	p value	Partial r (CI)	p value	Partial r (CI)	p value
Adjustments	None		confounders†		confounders†+ LVM		confounders†+ LVMI	
Left ventricular ejection fraction versus								
LVM_{inappr}	-0.25*(-0.33 to -0.18)	<0.0001	-0.41*(-0.47 to -0.34)	<0.0001	-0.52 (-0.57 to -0.46)	<0.0001	-0.52 (-0.57 to -0.46)	<0.0001
LVM	-0.04 (-0.12 to 0.04)	=0.33	-0.08 (-0.16 to -0.01)	=0.042	-	-	-	-
LVMI	-0.003 (-0.08 to 0.08)	=0.94	-0.07 (0.01 to 0.32)	=0.04	-	-	-	-
Left ventricular midwall fractional shortening versus								
LVM_{inappr}	-0.26*(-0.33 to -0.19)	<0.0001	-0.29*(-0.36 to -0.22)	<0.0001	-0.42 (-0.48 to -0.35)	<0.0001	-0.39 (-0.46 to -0.32)	<0.0001
LVM	-0.04 (-0.12 to 0.04)	=0.33	-0.02 (-0.10 to 0.06)	=0.69	-	-	-	-
LVMI	-0.04 (-0.12 to 0.04)	=0.30	-0.03 (-0.10 to 0. 06)	=0.54	-	-	-	-

*p<0.0001 vs correlation coefficients for LVM and LVMI. CI, confidence interval. †Adjustments are for age, sex, LV circumferential systolic wall stress, HbA1c, pulse rate, treatment for hypertension, regular smoking, regular alcohol intake, waist circumference and body height (when assessing relations with LVM). Probability values are further adjusted for non-independence of family members.

trend for an inverse association with EF and only after adjustments for confounders (Figure 4.2 and Table 4.7). Neither LVM, nor LVMI were associated with FSmid (Table 4.7).

The relationships between LVM_{inappr} and EF or FSmid were significantly stronger than the relationships between LVM or LVMI and EF or FSmid (Table 4.7)($p<0.0001$ for comparison of partial r values). Moreover, the relationships between LVM_{inappr} and EF or FSmid remained unchanged despite further adjustments for LVM or LVMI (Table 4.7). The relationships between LVM_{inappr} and EF also remained unchanged despite further adjustments for stroke volume (partial r= -0.43, confidence intervals= -0.49 to -0.37, $p<0.0001$) or LV end diastolic diameter (partial r= -0.47, confidence intervals= -0.53 to -0.40, $p<0.0001$). Replacing LV systolic wall stress with conventional, 24-hour, day, or night SBP showed similar relationships (data not shown). Secondary data analysis with adjustments for the use of ACEIs or β-blockers in place of "treatment for hypertension" produced essentially the same relationships (Table 4.8).

4.2.7 Relative impact of LVM, LVMI, or LVM_{inappr} on EF and the odds of a reduced EF at a community level.

With a number of factors included in a multivariate regression model, LVM_{inappr} was second only to LV systolic wall stress in contributing to EF at a community level, whilst LVM and LVMI contributed little (Table 4.9). In the community studied, 44 of 626 participants (7%) had an EF<55%. With adjustments for age, sex, LV systolic stress, HbA1c, pulse rate, treatment for hypertension, regular smoking, regular alcohol intake and waist circumference, an increased LVM_{inappr} was strongly associated with an odds of a reduced EF (<55%)(Odds ratio=6.85, confidence interval=2.99-15.68, $p<0.0001$). In contrast, an increased LVMI was not associated with an odds of a reduced EF (Odds ratio=1.32, confidence interval=0.60-2.92, p=0.50).

Table 4.8. Multivariate adjusted (including adjustments for the use of angiotensin-converting enzyme inhibitors [ACEI] and beta adrenergic receptor blockers [β-blockers]) relationships between indexes of left ventricular mass (LVM) and systolic function with LVM expressed as an inappropriate increase in LVM (LVM_{inappr}), absolute LVM or LVM indexed to height$^{2.7}$ (LVMI)(n=626).

	Partial r (CI)	p value	Partial r (CI)	p value	Partial r (CI)	p value
Adjustments	confounders†		confounders†+ LVM		confounders†+ LVMI	
Left ventricular ejection fraction versus						
LVM_{inappr}	-0.41 (-0.47 to -0.34)	<0.0001	-0.52* (-0.57 to -0.46)	<0.0001	-0.52 (-0.57 to -0.46)	<0.0001
LVM	-0.08 (-0.16 to -0.004)	=0.040	-	-	-	-
LVMI	-0.06 (-0.14 to 0.02)	=0.12	-	-	-	-
Left ventricular midwall fractional shortening versus						
LVM_{inappr}	-0.29 (-0.36 to -0.21)	<0.0001	-0.42* (-0.48 to -0.35)	<0.0001	-0.40 (-0.46 to -0.33)	<0.0001
LVM	-0.01 (-0.09 to 0.07)	=0.80	-	-	-	-
LVMI	-0.02 (-0.10 to 0.06)	=0.66	-	-	-	-

*p<0.0001 vs correlation coefficients for LVM and LVMI. CI, confidence interval. †Adjustments are for age, sex, LV systolic stress, HbA1c, pulse rate, the use of ACEIs and β-blockers, regular smoking, regular alcohol intake, waist circumference and body height (when assessing relations with LVM). Probability values are further adjusted for non-independence of family member.

Table 4.9. Comparison of the impact on left ventricular ejection fraction (EF) of factors related to systolic chamber function in a community sample (n=626).

Model with→	LVM_{inappr}		LVM		LVMI	
EF versus	β-coeff†±SEM	p-value	β-coeff†±SEM	p-value	β-coeff†±SEM	p-value
LVM_{inappr}	-0.40±0.04*	p<0.0001	-	-	-	-
LVM	-	-	-0.09±0.04	p<0.05	-	-
LVMI	-	-	-	-	-0.07±0.04	p=0.07
LV systolic wall stress	-0.53±0.03	p<0.0001	-0.47±0.04	p<0.0001	-0.47±0.04	p<0.0001
Age	-0.13±0.03	p<0.0001	-0.14±0.05	p<0.0001	-0.15±0.05	p<0.0001
Glycated haemoglobin	-0.07±0.04	p<0.05	-0.08±0.04	p<0.05	-0.09±0.04	p<0.05

β-coeff, standardised β-coefficients (slopes) of relationships; LVM_{inappr}, inappropriate increase in left ventricular mass; LVMI, LVM indexed for $height^{2.7}$. *p<0.0001 vs β-coefficients for LVM and LVMI. †Additional factors in the model not listed included sex, pulse rate, treatment for hypertension, regular smoking, regular alcohol intake and waist circumference. Probability values are further adjusted for non-independence of family members.

4.3 Discussion

The main findings of the present study are as follows: In a randomly selected community sample of black African ancestry, in contrast to a modest or a lack of relationship noted between LVM or LVMI and EF, an increased LVM_{inappr} was strongly and independently related to a decreased EF even with adjustments for LVM or LVMI. Moreover, the strength of the relationship between LVM_{inappr} and EF was greater than that of the relations between LVM or LVMI and EF. In a multivariate model with all potential determinants of EF included in the model, LVM_{inappr} was second only to LV systolic wall stress in contributing toward EF at a community level and was strongly and independently associated with a reduced EF. Furthermore, indices of excess adiposity were the principle factors independently associated with LVM_{inappr} and these relationships were beyond conventional BP, 24-hour BP, systolic wall stress and aortic PWV.

To-date whether inverse relationships exist between LVM_{inappr} and LV systolic chamber function beyond that of absolute or indexed LVM is uncertain. In previous studies reporting on such relations (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) only in the Losartan Intervention For Endpoint Reduction (LIFE) study did the authors compare the relationships between LV systolic chamber function and either LVM_{inappr} or LVM (Palmieri et al 2001). In this regard, they noted that LVM was equally as strongly related to EF as LVM_{inappr}, but they did not evaluate whether the LVM_{inappr}-EF relationship persisted with adjustments for LVM or LVMI (Palmieri et al 2001). However, the LIFE study consisted of a select patient group in that only participants with electrocardiographic evidence of LVH were recruited. Thus, mean LVM values in either the group of patients with increased or normal LVM_{inappr} were markedly higher (227-271g) in the LIFE (Palmieri et al 2001) than in the present (145-202g) study. In addition, mean LV systolic myocardial function (FSmid) values were lower in the LIFE (13.7-16.5%) (Palmieri et al 2001) as compared to the present (20.9-23.5%) study. The LIFE study may therefore have selected for a group of participants with

marked LVH and a higher risk of LV systolic dysfunction. Under these circumstances, relationships between absolute LVM and EF may have been more robust and difficult to distinguish from those between LVM_{inappr} and EF. Irrespective of the reasons for the apparent discrepancy between the LIFE (Palmieri et al 2001) and the present study, the present study provides clear evidence that LVM_{inappr} is inversely related to EF beyond LVM or LVMI and hence supports the notion that LVH is a compensatory response to workload, but when exceeding that predicted by workload, is associated with LV systolic chamber decompensation.

Although a number of studies have demonstrated inverse relations between LVM_{inappr} and LV systolic chamber 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), in some prior studies (Mureddu et al 2001, Palmieri et al 2004, Mureddu et al 2009) the existence of these relationships is less clear. In two prior studies (Mureddu et al 2001, Palmieri et al 2004) although EF was reduced in hypertensives without LVH but with an increased LVM_{inappr}, EF was not reported as being correlated with LVM_{inappr}. Moreover, in an alternative study (Mureddu et al 2009) although LV systolic chamber function was markedly reduced in patients with an increased LVM_{inappr}, in a multivariate model LV systolic chamber function was not reported as being independently correlated with LVM_{inappr}. In contrast to the apparently inconsistent relations between LVM_{inappr} and systolic chamber 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, Mureddu et al 2001, Palmieri et al 2004, Mureddu et al 2009), stress-corrected midwall fractional shortening (FSmid), a measure of LV systolic myocardial function, has nevertheless consistently been shown to be inversely related to LVM_{inappr} (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, Mureddu et al 2001, Palmieri et al 2004, Mureddu et al 2009). It is therefore possible that under certain circumstances, although LVM in excess of that predicted by stroke work is associated with a reduced systolic myocardial function, that the hypertrophy is in-part compensatory in nature in that it

contributes toward maintaining LV chamber function in the face of deteriorating myocardial function. Only prospective studies evaluating the evolution of systolic functional changes in the transition from appropriate to inappropriate LVH and subsequent LV systolic chamber dysfunction will answer this question.

In studies where inverse LVM_{inappr}-LV systolic chamber function relations have previously been demonstrated (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), the authors have not adjusted for wall stress (afterload), the principal determinant of LV systolic function, or other determinants of LV systolic function, such as heart rate. Indeed, a reduced EF has been reported in patients with an increased LVM_{inappr} who were also noted to have an increased LV wall stress (de Simone et al 2004). As indicated in the present study, LV systolic wall stress is the major determinant of EF at a community level. An increased wall stress could thus explain previously reported decreases in EF or LV systolic chamber 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), at least in patients with an increased LVM_{inappr} (de Simone et al 2004). In contrast, in the present study I show clear inverse relations between LVM_{inappr} and EF independent of LV wall stress, conventional and ambulatory BP, and alternative confounders such as heart rate.

Although a number of studies conducted in select clinical samples have demonstrated an increased BMI in those with inappropriate LVH (Palmieri et al 1999, Palmieri et al 2001, Calentano et al 2001, Palmieri et al 2004, de Simone et al 2004, Chinali et al 2006, Lopez et al 2007, Chinali et al 2007, Ratto et al 2008), these associations were not adjusted for confounders and in other select study samples (de Simone et al 2001, Mureddu et al 2001, Muiesan et al 2007, Cioffi et al 2011) obesity was not related to LVM_{inappr} even in unadjusted models. Clearly the use of select samples raises the question of a selection bias. In contrast, in the present unselected community-based sample with a high prevalence of obesity I show that BMI and waist circumference were strongly and independemtly associated with LVM_{inappr} and this relationship was noted beyond a number of

additional haemodynamic effects including systolic wall stress, 24-hour BP and aortic PWV. Thus, the results of the present study provide strong evidence that obesity produces increases in LVM beyond stroke work and a number of alternative haemodynamic factors. The potential mechanisms of this effect were further evaluated in Chapter 6 of the present thesis.

Importantly, our group have recently demonstrated that estimated glomerular filtration rate is strongly related to LVMI and LVM_{inappr} (Maunganidze et al 2013) and there is now substantial evidence that obesity may impair renal function. This raises the question of whether obesity may mediate increases in LVM_{inappr} through effects on renal mechanisms. However, in the present study sample we have not been able to show that indices of excess adiposity are related to decreases in glomerular filtration rate (Maunganidze et al 2013). Hence, it is unlikely that the relationship between adiposity indices and LVM_{inappr} may be mediated through alterations in renal function.

The potential clinical implications of the present study warrant consideration. Pending validation of the present results in prospective, intervention studies and with heart failure with a reduced EF as an outcome, the results of the present study suggest that LVM_{inappr} may complement the use of LVMI when risk predicting or when assessing LVH regression with therapy. Future prospective studies evaluating the impact of regression of increases in LVM_{inappr} independent of absolute LVM or LVMI on the development of heart failure with a reduced EF are therefore required. The most appropriate approach to producing regression of inappropriate LVH may depend on the mechanisms that mediate obesity-induced increases in LVM_{inappr}. In this regard, in chapter 6 I provide further evidence to suggest a potential mechanism.

The limitations of the present study are as follows: The present study was a cross-sectional study and hence does not allow us to draw conclusions regarding cause and effect. Thus, the inverse LVM_{inappr}-EF relationships could be attributed to compensatory increases in LVM following LV systolic dysfunction rather than *vice versa*, or to residual confounding effects. However, recent evidence as presented in chapter 5 of the present thesis,

demonstrating that decreases in LVM_{inappr} with antihypertensive therapy are strongly related to on-treatment increases in EF beyond changes in LVM and LVMI suggests that LVM_{inappr} may indeed cause a decrease in EF (Woodiwiss and Libhaber et al 2012). Second, the present study was conducted in one ethnic group (black African descent) with a high prevalence of LVM_{inappr} and with higher thresholds for an increased LVM_{inappr} determined in a healthy sample, than that previously reported on in other ethnic groups. However, the thresholds for LVM_{inappr} corresponded to thresholds of LVMI of 51.8 $g/m^{2.7}$ in the healthy sample, an accepted threshold for LVMI in this ethnic group (Nunez et al 2005). Third, we determined LVM_{inappr} using predicted LVM values calculated from a formula derived in an alternative population (de Simone et al 2002). However, in support of the suitability of the calculation of LVM_{inappr} in the community studied, in contrast to strong positive correlations noted between LVM (or LVMI) and stroke work, when LVM was expressed as LVM_{inappr}, no residual relations with stroke work were observed. Fourth, LV ejection fraction was measured with echocardiography whilst magnetic resonance imaging (MRI) measurements of systolic function have been demonstrated to be more sensitive for predicting cardiovascular events (Mewton et al 2013). It is therefore possible that we may have demonstrated stronger relationships between LVMI and LV ejection fraction if magnetic resonance imaging had been employed. Last, relatively weak r values were noted for relationships between LVM_{inappr} and LV ejection fraction, or between indices of obesity and LVM_{inappr}, findings that must be interpreted with caution. This may reflect overall weak relationships or an inability to appropriately account for all confounders or to exclude the impact of co-linearity between adjustors in multivariate models. Importantly, in multivariate models, with all adjustments including LVMI, the relationship (partial r, CI) between LVM_{inappr} and left ventricular ejection fraction was strong (-0.52, -0.57 to -0.46, $p<0.0001$). Nevertheless, only intervention studies are likely to reveal the actual magnitude of the effect of obesity on LVM_{inappr} or LVM_{inappr} on LV ejection fraction if indeed these relationships are cause and effect. In this regard, in the subsequent chapter (chapter 5) I show that the relationship (partial r value) between on-treatment change in LVM_{inappr} and increase in left

ventricular ejection fraction in mild-to-moderate hypertensives was -0.63 (-0.71 to -0.52) (<0.0001), thus providing the evidence to suggest the size effect of LVM_{inappr} on left ventricular ejection fraction is indeed substantial.

In conclusion, in the present study I show that in a community sample of black African ancestry, LVM in excess of that predicted by LV work load (LVM_{inappr}) is strongly and inversely related to EF independent of and more strongly than LVM or LVMI. Moreover, at a community level obesity is the major determinant of LVM_{inappr}.These data therefore support the view that LVH, as indexed by LVM or LVMI incorporates a component of LVH that can be viewed as a compensatory change that preserves EF, but when this exceeds that predicted by LV workload, this excess in LV growth is associated with a decrease in EF. This excess in LV growth appears to be largely driven by obesity-induced effects independent of haemodynamic factors.

CHAPTER 5

Relationship Between On-Treatment Decreases in Inappropriate Versus Absolute or Indexed Left Ventricular Mass and Increases in Ejection Fraction in Hypertension.

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

As acknoweldged in the paper, my contribution was equal to that of the first authors.

Abstract

Although in cross-sectional studies left ventricular mass (LVM) which exceeds that predicted by work load (inappropriate LVM [LVM_{inappr}]), but not absolute LVM or LVM index (LVMI), is inversely related to LV ejection fraction (EF), whether on-treatment decreases in LVM_{inappr} (%observed/predicted LVM) account for increases in EF beyond LVM or LVMI is unclear. Echocardiography was performed in 168 mild-to-moderate hypertensives treated for 4 months. Although in patients with an LVMI>51g/$m^{2.7}$ (n=112)(change in LVMI=-13.7±14.0 g/$m^{2.7}$, p<0.0001), but not in patients with an LVMI≤51g/$m^{2.7}$(n=56)(change in LVMI=1.3±9.3 g/$m^{2.7}$) LVMI decreased with treatment; treatment failed to increase EF in either group (1.2±10.8% and 2.7±10.7% respectively). In contrast, in patients with inappropriate LV hypertrophy (LVH) (LVM_{inappr}>150%, n=33) LVM_{inappr} decreased (-32±27%, p<0.0001) and EF increased (5.0±10.3%, p<0.0001) after treatment, whilst in patients with a LVM_{inappr}≤150% (n=135), neither LVM_{inappr} (-0.5±23%), nor EF (0.9±10.3%) changed with therapy. With adjustments for circumferential LV wall stress and other confounders, whilst on-treatment decreases in LVM or LVMI were weakly related to an attenuated EF (partial r=0.17, p<0.05), on-treatment decreases in LVM_{inappr} were strongly related to increases in EF even after further adjustments for LVM or LVMI (partial r=-0.63, confidence interval=-0.71 to -0.52, p<0.0001). In conclusion, decreases in LVM_{inappr} are strongly related to on-treatment increases in EF beyond changes in LVM and LVMI. LVH can therefore be viewed as a compensatory change that preserves EF, but when in excess of that predicted by stroke work, as a pathophysiological process accounting for a reduced EF.

5.0 Introduction

Left ventricular hypertrophy (LVH) is a predictor of heart failure (Casale et al 1986, Levy et al 1990, Ghali et al 1992, Levy et al 1996, Gottdiener et al 2000, Gardin et al 2001, Aurigemma et al 2001) and the development of a reduced ejection fraction (EF)(Drazner et al 2004) independent of myocardial infarction. Left ventricular mass (LVM) may therefore determine the progression to heart failure with a reduced rather than a preserved EF Drazner 2011, Bibbins-Domingo et al 2009). However, as highlighted in the previous chapter, in-keeping with the classical tenet that LVH is a compensatory response to LV load, an increased LVM (Aurigemma et al 1995, de Simone[a] et al 1994, Shimizu et al 1991) or on-treatment decreases in LVM (Perlini et al 2001) have been associated with an unchanged EF. Moreover, LVH may even be associated with an enhanced EF for that predicted by wall stress (Hartford et al 1985) and on-treatment decreases in LVM have been related to reductions rather than increases in indices of systolic LV chamber function (Wachtell et al 2002). There is therefore considerable uncertainty as to whether LVH contributes to decreases in systolic chamber function.

One possibility that may explain discrepancies in the ability to show consistent relations between LVM or LVM index (LVMI) and a reduced systolic LV chamber function (Aurigemma et al 1995, de Simone[b] et al 1994, Shimizu et al 1991, Perlini et al 2001, Hartford et al 1985, Wachtell et al 2002) is that absolute LVM and LVMI may incorporate a component of LVH considered compensatory in nature, whilst there may also be a component of LVH that contributes to decompensation. In this regard, LVM in excess of that predicted by work load (i.e. stroke work=blood pressure x stroke volume) termed “inappropriate LVM” (LVM_{inappr})(de Simone et al 1998) is inversely associated with systolic LV chamber 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, Muiesan et al 2007). However, these relationships have largely been demonstrated in cross-sectional studies (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) and are at odds with on-treatment decreases in systolic LV chamber function associated with LVH regression (Wachtell et al 2002). Inverse LVM_{inappr}–LV systolic chamber function relations (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) may therefore reflect compensatory increases in LVM as a consequence of systolic dysfunction or associated confounding effects. Although one prior study has reported that on-treatment regression but not persistence of LVM_{inappr} is associated with an improved EF (Muiesan et al 2007), whether increases in EF in the participants showing regression of LVM_{inappr} in that study was independent of or stronger than changes in LVM or LVMI is uncertain. To further explore the possibility that increases in LVM beyond workload and absolute LVM may contribute toward a decreased systolic LV chamber function, in the present study I therefore aimed to evaluate whether treatment-induced decreases in LVM_{inappr} in mild-to-moderate hypertension are associated with increases in EF independent of and more strongly than LVM or LVMI.

5.1 Methods

5.1.1 Study group.

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M940106). Participants gave informed, written consent. The study design has previously been described (Sareli et al 2001, Skudicky et al 2002). Hypertensives of black African descent 18-70 years of age, free of clinically significant cardiovascular and non-cardiovascular disease, were enrolled. Hypertension was diagnosed after a 2-week placebo run-in period, if daytime ambulatory diastolic blood pressure (BP) was 90-114 mm Hg.

Eligible patients were randomized to receive nifedipine gastrointestinal system (GITS) 30mg/d, verapamil slow release (SR) 240 mg/d, hydrochlorothiazide 12.5 mg/d or enalapril 10 mg/d and patients were followed up at monthly intervals for 4 months (Sareli et al 2001). At each monthly visit uptitration of therapy or the addition of therapy occurred as described (Sareli et al 2001). If target BP was not achieved (daytime diastolic BP<90 mm Hg), at 1 month the daily dose of therapy was increased (nifedipine GITS, 60 mg, verapamil SR, 360 mg, hydrochlorothiazide 25 mg and enalapril 20 mg), and at 2 months in patients receiving nifedipine GITS, either enalapril 10 mg/d, carvedilol 25 mg/d, or verapamil SR were added or the dose of nifedipine GITS was increased to 90 mg/d. In patients receiving verapamil SR at 2 months the dose could be increased to 480 mg/d. In those receiving hydrochlorothiazide 25 mg/d, reserpine 0.125 mg/d could be added and in those receiving enalapril 20 mg/d, hydrochlorothiazide 12.5 mg/d could be added.

Of the 409 patients randomised, 233 were eligible for inclusion in the substudy because echocardiograms were of sufficient quality. Of the latter patients, 23 were withdrawn before 4 months and 42 did not have all measurements. Thus, data in 168 participants were available for analysis. High quality echocardiograms could not be obtained in 176 participants due to the high participant rate of obese females with a generalised fat distribution, including the thoracic region.

5.1.2 Blood pressure.

High quality conventional BP measurements were obtained by trained nurse-technicians according to guidelines (O'Brien et al 2003, Pickering et al 2005) using a standard mercury sphygmomanometer as previously described (Sareli et al 2001, Skudicky et al 2002). Ambulatory 24-hour, day and night BP were determined using SpaceLabs monitors (model 90207) as previously described (Sareli et al 2001, Skudicky et al 2002).

5.1.3 Echocardiography.

M-mode, 2-dimensional, pulse and colour Doppler echocardiography was performed as previously described (Sareli et al 2001, Skudicky et al 2002)(see chapter 2, pages 47-55 for further details) and M-mode variables were analysed according to the American Society of Echocardiography convention (Sahn et al 1978). All participants were assessed for mitral valve abnormalities as determined using 2-dimensional and color Doppler imaging. All measurements were recorded and analyzed off-line by experienced investigators whom were unaware of the clinical data of the participants. Left ventricular mass (LVM) was determined using a standard formula (Devereux et al 1986) as described in chapter 2, page 54 and indexed (LVMI) to height$^{2.7}$. LV mean wall thickness was calculated as the mean of septal+posterior wall thickness and LV relative wall thickness as (septal+posterior wall thickness)/LV end diastolic diameter. An LVMI >51 g/m$^{2.7}$ was considered to be increased (Nunez et al 2005). Left ventricular ejection fraction (EF) and midwall fractional shortening (FSmid) were calculated to determine LV chamber and myocardial systolic function respectively using standard formulae as described in chapter 2, page 54 and chapter 4, page 95. The calcution of FSmid using a modified ellipsoidal model as previously described (de Simone[b] et al 1996) accounts for epicardial migration of the midwall during systole. Stroke volume was evaluated from the difference between LV end diastolic and systolic volumes determined using both the Teichholz (Teichholz et al 1976) and the Z-derived (de Simone[c] et al 1996) methods (see chapter 2, page 54). Circumferential LV systolic wall stress was calculated as described in chapter 4, page 95 (Shimizu et al 1991). As described in chapter 4, page 96 the extent of inappropriate LVM (LVM_{inappr}) was determined from predicted LVM as described by others (de Simone et al 2002), where predicted LVM was calculated as 55.37+(6.64 x height$^{2.7}$)+(0.64 x [systolic BP x stroke volume x 0.014]) –(18.07 x gender), where male gender=1 and female gender=2, and where stroke volume was calculated from LV volumes assessed from the Z-derived method. Inappropriate LVM was expressed either as actual-predicted LVM in grams, or % actual LVM/predicted LVM. An

$LVMI_{inappr}$>150% was considered to be increased. This threshold was identified from the upper 95% confidence interval for $LVMI_{inappr}$ determined in 140 of 678 participants from a community-based study without clinically significant disease and normal blood parameters who were normotensive, non-diabetic, and had a BMI<30 kg/m^2. In these participants the upper 95% confidence for LVMI was 51.8 $g/m^{2.7}$.

5.1.4 Data analysis.

Database management and statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Continuous data are reported as mean±SD. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. Changes in variables over the 4 month treatment period and a comparison of these changes between groups with versus without increases in LVM_{inappr} or LVMI were determined using a two-way ANOVA with a Tukey *post hoc* test. A comparison of changes in adjusted EF between groups with and without increases in LVM_{inappr} or LVMI was determined using multivariate regression analysis. Independent relations between baseline or change in LVM, LVMI or LVM_{inappr} and baseline or change in EF were assessed from multivariate linear regression analysis with appropriate adjustors. Adjustments included age, sex, circumferential LV systolic wall stress, diabetes mellitus, pulse rate, previous treatment for hypertension, regular smoking, regular alcohol intake and body weight as in bivariate or multivariate models these parameters were associated with EF, LVM, LVMI, or LVM_{inappr}. The use of carvedilol was also included as an adjustor as a modestly higher proportion of participants with an increased LVM_{inappr} were receiving this agent. Z-Statistics were used to compare correlation coefficients.

5.2 Results

5.2.1 Participant characteristics.

A high proportion of participants were obese (Table 5.1). 19.6% had inappropriate increases in LVM and 66.7% had LVH (LVMI>51 g/$m^{2.7}$). As compared to the 176 non-participants, the 168 participants who had all data available for analysis were younger and less obese (Table 5.1). Otherwise participants with data available had similar characteristics as compared to non-participants, including similar conventional and ambulatory BP values (Table 5.1).

5.2.2 Suitability of the LVM_{inappr} calculation.

In contrast to strong positive correlations between LVM (or LVMI) and stroke work (r=0.56-0.60, p<0.0001), LVM_{inappr} was unrelated to stroke work (r=0.001, p=0.99).

5.2.3 Clinical and demographic factors at baseline independently associated with LVM_{inappr}.

On bivariate analysis age, female gender, regular alcohol intake, BMI and body weight were positively associated with LVM_{inappr} at baseline (p<0.05-<0.0001). In a multivariate model gender (p<0.05), BMI (p<0.0001), and body weight (p<0.0001) (separate model from BMI) were independently and positively related to LVM_{inappr}.

5.2.4 Relationships between LV systolic function and LVM_{inappr}, LVM or LVMI at baseline.

Strong relationships between baseline LVM_{inappr} and both baseline EF and FSmid independent of confounders and either LVM or LVMI were noted (Table 5.2). In contrast,

Table 5.1. Participant and non-participant characteristics at baseline

	Participants	Non-participants
Number (% women)	168 (77.4)	176 (78.4)
Age (years)	51±10	56±9**
Body mass index (kg/m^2)	30.4±6.1	32.3±7.4*
% Overweight/obese	25.6/52.4	28.6/56.0
% Diabetes mellitus	7.1	7.9
% Regular smoking	12.5	14.8
% Regular alcohol	19.1	25.0
Conventional systolic BP/ diastolic BP (mm Hg)	171±20/102±8	173±19/103±7
24-hour systolic BP/diastolic BP (mm Hg)	151±15/96±7	150±15/95±7
Day systolic BP/diastolic BP (mm Hg)	155±14/101±7	155±14/101±7
Night systolic BP/diastolic BP (mm Hg)	146±17/91±9	145±17/89±9

BP, blood pressure. *p<0.01, **p<0.0001 vs participants.

Table 5.2. Relationships between baseline indexes of left ventricular mass (LVM) and baseline LV ejection fraction (EF) or LV midwall fractional shortening (FSmid) with LVM expressed as an inappropriate increase in LVM (LVM_{inappr}), absolute LVM or LVM indexed to $height^{2.7}$ (LVMI) in mild-to-moderate hypertension (n=168).

	Adjustors*	Partial r	Confidence intervals	p values
Baseline EF versus				
LVM_{inappr}	*+LVM	-0.61	-0.70 to -0.50	<0.0001
LVM_{inappr}	*+LVM	-0.62	-0.70 to -0.51	<0.0001
LVM	*	-0.05	-0.20 to 0.11	=0.56
LVMI	*	-0.01	-0.16 to 0.15	=0.91
Baseline FSmid versus				
LVM_{inappr}	*+LVM	-0.39	-0.51 to -0.24	<0.0001
LVM_{inappr}	*+LVM	-0.36	-0.49 to -0.32	<0.0001
LVM	*	0.08	-0.08 to 0.23	=0.33
LVMI	*	0.08	-0.08 to 0.23	=0.33

* Adjustors are for age, sex, circumferential LV systolic stress, diabetes mellitus, pulse rate, previous treatment for hypertension, regular smoking, regular alcohol intake, body weight, and body height (when assessing relations with LVM).

neither baseline LVM nor LVMI were independently related to either baseline EF or FSmid (Table 5.2).

5.2.5 Treatment effects in the whole group.

Four months of antihypertensive therapy in all participants resulted in decreases in conventional and ambulatory BP, LV wall stress, stroke work, LVM, LVMI, and LVM_{inappr} (Table 5.3) and a modest increase in EF, but no changes in FSmid or LV relative wall thickness (Table 5.3).

5.2.6 Treatment effects on BP, wall stress and stroke work in patients with or without an increased LVM_{inappr} or LVMI.

At the end of the 4 month treatment period, participants with an increased LVM_{inappr} or LVMI were receiving similar drug classes as compared to participants with an appropriate LVM or normal LVMI except for a modestly greater use of carvedilol in the group with an increased LVM_{inappr} (Table 5.4). Antihypertensive treatment of participants with an increased LVM_{inappr} resulted in decreases in conventional or 24-hour BP and LV systolic wall stress and stroke work which were not statistically different from those noted in participants with an appropriate LVM (Table 5.5). However, as compared to participants with a normal LVMI, antihypertensive treatment of participants with an increased LVMI resulted in greater decreases in systolic BP and stroke work (Table 5.5).

5.2.7 Treatment effects on LV structure in patients with or without an increased LVM_{inappr} or LVMI.

Treatment of participants with an increased LVM_{inappr} or LVMI resulted in decreases in all LV structural parameters (Table 5.6). In participants with an appropriate LVM,

Table 5.3. Changes in hemodynamic and left ventricular variables after 4 months of antihypertensive treatment in mild-to-moderate hypertensives (n=168).

	0 months	4 months	Change in
Conventional systolic BP (mm Hg)	171±20	147±21**	-24±25
Conventional diastolic BP (mm Hg)	102±8	92±11**	-11±13
24-hour systolic BP (mm Hg)	151±15	129±14**	-22±15
24-hour diastolic BP (mm Hg)	96±7	83±8**	-14±9
LV systolic wall stress (g/cm2)	135±34	115±31**	-20±40
Stroke work (g-m)	150±48	123±39**	-26±51
LV mass (LVM) (g)	209±65	179±50**	-30±50
LVM indexed for height$^{2.7}$ (g/m$^{2.7}$)	60.4±18.6	51.7±13.8**	-8.7±14.5
% Actual LVM/Predicted LVM	123±31	117±26*	-6±28
Actual LVM-predicted LVM (g)	38.3±54.1	25.6±41.0*	-12.7±42.5
LV relative wall thickness	0.50±0.12	0.48±0.11	-0.02±0.14
LV ejection fraction (EF) (%)	63.2±9.1	64.9±9.7*	1.7±10.7
LV midwall fractional shortening (%)	19.6±5.3	19.5±5.3	-0.06±6.7

*p<0.05, **p<0.0001 versus 0 months (paired Student's t-test).

Table 5.4. Antihypertensive drug classes at the end of 4-months of therapy, received by participants with an increased or normal inappropriate increase in left ventricular mass (LVM_{inappr}) or LVM index (LVMI) at baseline.

	LVM_{inappr} (%)		LVMI ($g/m^{2.7}$)	
	>150 (n=33)	≤150 (n=135)	>51 (n=112)	≤51 (n=56)
Hydrochlorothiazide (n, [%])	8 (24)	40 (30)	33 (29)	15 (27)
Nifedipine GITS (n, [%])	22 (67)	80 (59)	68 (61)	34 (61)
Enalapril (n, [%])	5 (15)	25 (19)	16 (14)	14 (25)
Verapamil SR (n, [%])	6 (18)	31 (23)	24 (21)	13 (23)
Reserpine (n, [%])	1 (3)	10 (7)	7 (6)	4 (7)
Carvedilol (n, [%])	6 (18)*	7 (5)	9 (8)	4 (7)

GITS, gastrointestinal system, SR, slow release. *$p<0.05$ vs LVM_{inappr} ≤150%.

Table 5.5. Changes in conventional and ambulatory blood pressure (BP), left ventricular wall stress and stroke work with antihypertensive treatment in mild-to-moderate hypertensives (n=168) with or without inappropriate increases in left ventricular mass (LVM_{inappr}) or LVM index (LVMI) at baseline.

	0 months	4 months	Change in	% Change	0 months	4 months	Change in	% Change
Baseline LVM_{inappr}	Inappropriate LVM (LVM_{inappr} >150%) (n=33)				Appropriate LVM (LVM_{inappr} ≤150%) (n=135)			
Conventional systolic BP (mm Hg)	172±20	154±27*	-18±26	-10.1±15.1	171±20	146±19*	-25±25	-14.1±13.9
Conventional diastolic BP (mm Hg)	102±8	95±12*	-7±14	-6.1±14.0	103±9	91±11*	-12±13	-10.9±12.6
24-hour systolic BP (mm Hg)	152±14	133±20*	-19±16	-12.4±10.1	150±15	128±13*	-23±15	-14.5±8.8
24-hour diastolic BP (mm Hg)	97±7	85±11*	-12±9	-12.7±9.0	96±7	82±8*	-14±9	-14.2±8.7
LV systolic wall stress (g/cm^2)	132±40	115±35*	-17±45	-12.6±22.5	135±33	115±31*	-21±39	-15.0±24.4
Stroke work (g-m)	153±53	135±52*	-18±56	-11.1±34.4	149±47	121±35*	-29±50	-17.2±25.6
Baseline LVMI	>51 $g/m^{2.7}$ (n=112)				≤51 $g/m^{2.7}$ (n=56)			
Conventional systolic BP (mm Hg)	176±19	148±23*	-27±25†	-14.9±13.4†	163±18	145±18*	-18±26	-10.1±15.3
Conventional diastolic BP (mm Hg)	103±8	92±12*	-12±14	-10.7±13.1	101±8	92±10*	-9±12	-8.4±12.8
24-hour systolic BP (mm Hg)	153±15	130±16*	-23±15	-14.8±9.1	145±13	126±10*	-19±14	-12.6±9.0
24-hour diastolic BP (mm Hg)	97±7	83±9*	-14±9	-14.3±8.4†	95±7	82±10*	-13±10	-13.2±9.5
LV systolic wall stress (g/cm^2)	135±33	114±31*	-21±40	-14.6±25.1	134±36	115±32*	-19±40	-14.7±24.5
Stroke work (g-m)	162±48	128±43*	-34±53††	-20.1±25.6††	126±38	115±30*	-11±42	-8.2±28.0

* $p<0.0001$ as compared to 0 months. †$p<0.05$, ††$p<0.005$ as compared to values in groups without an increased LVM_{inappr} or LVMI (interactive effect).

Table 5.6. Changes in left ventricular (LV) structure with antihypertensive treatment in mild-to-moderate hypertensives (n=168) with or without inappropriate increases in left ventricular mass (LVM_{inappr}) or LVM index (LVMI) at baseline.

	0 months	4 months	Change in	% Change	0 months	4 months	Change in	% Change
Baseline LVM_{inappr}	Inappropriate LVM (LVM_{inappr} >150%) (n=33)				Appropriate LVM (LVM_{inappr} ≤150%) (n=135)			
LV mass (LVM) (g)	287±70	217±62**	-70±51†††	-25.0±14.9†††	190±46	170±40*	-20±43	-8.2±21.5
LVM indexed for height$^{2.7}$ (g/m$^{2.7}$)	80±19	60±15**	-20±15†††	-25.0±14.9†††	55±14	50±12	-6±12	-8.2±21.5
LV mean wall thickness (cm)	1.41±0.15	1.21±0.14*	-0.19±0.14†††	-14.7±9.3†††	1.12±0.16	1.07±0.14	-0.05±0.17	-3.5±15.0
LV relative wall thickness	0.58±0.13	0.51±0.09*	-0.07±0.12†	-12.8±18.9†	0.48±0.11	0.48±0.10	-0.004±0.12	-2.0±25.0
LV end diastolic diameter (cm)	4.92±0.64	4.62±0.64*	-0.36±0.62†	-6.6±12.5†	4.58±0.51	4.44±0.50	-0.14±0.54	-2.6±11.3
% Actual LVM/Predicted LVM (LVM_{inappr})	169±22	137±30*	-32±27†††	-20.1±15.0†††	112±20	112±22	-0.5±23	-0.3±18.5
Actual LVM-predicted LVM (g)	117±47	58±53*	-59±38†††	-55.0±32.8†††	19±35	18±33	-1±35	-6.4±121.0
Baseline LVMI	>51 g/m$^{2.7}$ (n=112)				≤51 g/m$^{2.7}$ (n=56)			
LV mass (LVM) (g)	236±61	189±55*	-46±48†††	-18.4±17.6†††	155±30	159±29	4±33	3.1±21.4
LVM indexed for height$^{2.7}$ (g/m$^{2.7}$)	69.4±16.0	55.7±14.0*	-13.7±14.0†††	-18.4±17.6†††	42.2±6.2	43.6±8.8	1.3±9.3	3.1±21.3
LV mean wall thickness (cm)	1.25±0.17	1.13±0.16*	-0.12±0.16†††	-9.1±12.5†††	1.04±0.16	1.05±0.13	0.01±0.17	1.9±16.1
LV relative wall thickness	0.51±0.12	0.49±0.11*	-0.03±0.13	-4.5±21.2	0.47±0.12	0.47±0.10	0.001±0.14	-0.3±24.0
LV end diastolic diameter (cm)	4.78±0.56	4.52±0.59*	-0.25±0.61††	-4.9±11.9††	4.38±0.49	4.37±0.44	-0.01±0.46	-0.1±10.2

* p<0.01 *p<0.0001 as compared to 0 months. †p<0.05, ††p<0.005, †††p<0.0001 as compared to values in groups without an increased LVM_{inappr} or LVMI (interactive effects).

treatment also decreased LVM, LVMI, LV mean wall thickness, and LV end diastolic diameter, but not relative wall thickness, LVM_{inappr} or actual LVM-predicted LVM (Table 5.6). The decrease in LVM, LVMI, LV mean wall thickness, LV relative wall thickness and LVM_{inappr} or actual LVM-predicted LVM with treatment was greater in participants with an increased LVM_{inappr} as compared to those with an appropriate LVM (Table 5.6). In participants with a normal LVMI, treatment did not alter LV structure and treatment-induced decreases in LVM, LVMI, LV mean wall thickness and LV end diastolic diameter were greater in participants with an increased LVMI than those without (Table 5.6).

5.2.8 Treatment effects on LV systolic function in patients with or without an increased LVM_{inappr} or LVMI.

As compared to patients with an appropriate LVM, where unadjusted and multivariate adjusted EF failed to improve with antihypertensive therapy, in patients with an increased LVM_{inappr}, unadjusted and multivariate adjusted EF increased with antihypertensive therapy (Table 5.7). In contrast, no significant unadjusted or multivariate adjusted changes in EF were noted in patients with either an increased or a normal LVMI (Table 5.7). No significant treatment effects on FSmid were noted (Table 5.7).

5.2.9 Relationship between on-treatment change in LVM, LVMI, or LVM_{inappr} and LV EF.

With or without adjustments for potential confounders, on-treatment decreases and % decreases in $LVMI_{inappr}$ were strongly associated with an increase and % increase in EF (Figure 5.1 and Table 5.8). The strength of the multivariate adjusted relationships was unchanged with further adjustments for baseline EF included in the model (Table 5.8). In contrast, decreases and % decreases in LVM and LVMI were modestly associated with a decrease and % decrease in EF (Table 5.8). The positive relationships between LVM or LVMI and EF were abolished with further adjustments for baseline EF (Table 5.8). The

Table 5.7. Changes in left ventricular (LV) systolic function with antihypertensive treatment in mild-to-moderate hypertensives (n=168) with or without inappropriate increases in left ventricular mass (LVM_{inappr}) or LVM index (LVMI) at baseline.

	0 months	4 months	Change in	0 months	4 months	Change in
Baseline LVM_{inappr}	Inappropriate LVM (LVM_{inappr} >150%) (n=33)			Appropriate LVM (LVM_{inappr} ≤150%) (n=135)		
LV ejection fraction (%)	57.8±1.5	62.0±1.7	4.95±1.83†*	64.5±0.8	65.5±0.8	0.90±0.89
Adjusted# LV ejection fraction (%)	58.0±1.4	61.8±1.5	4.99±1.72†*	64.5±0.6	65.7±0.7	0.89±0.80
LV midwall fractional shortening (%)	17.5±0.9	17.2±0.9	-0.26±1.18	20.1±0.5	20.1±0.4	-0.05±0.58
Baseline LVMI		>51 g/$m^{2.7}$ (n=112)			≤51 g/$m^{2.7}$ (n=56)	
LV ejection fraction (%)	63.4±0.9	64.7±0.9	1.21±1.01	62.8±1.2	65.5±1.3	2.67±1.43
Adjusted# LV ejection fraction (%)	63.5±0.7	64.5±0.8	0.63±0.86	65.8±1.2	65.8±1.2	2.65±1.25
LV midwall fractional shortening (%)	20.0±0.5	19.5±0.5	-0.51±0.63	18.8±0.7	19.6±0.7	0.85±0.89

Data are expressed as mean±SEM. *p<0.05 as compared to change in the group without an increased LVM_{inappr}; †p<0.01 as compared to zero. #Adjustments are for age, sex, LV systolic stress, diabetes mellitus, pulse rate, previous treatment for hypertension, regular smoking, regular alcohol intake, body weight and carvedilol therapy.

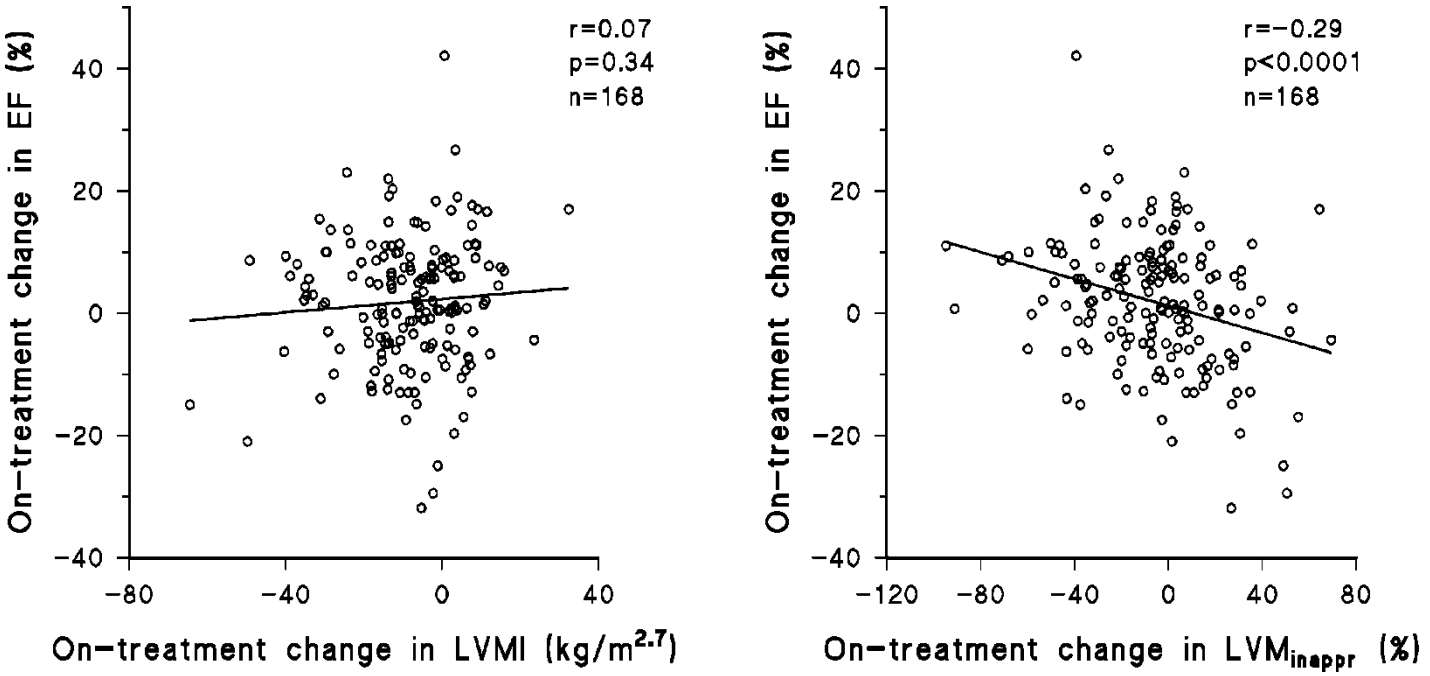


Figure 5.1 Bivariate relationships between on-treatment changes in left ventricular mass index (LVMI) or inappropriate LVM (LVM_{inappr}) and LV ejection fraction (EF) in hypertensives.

Table 5.8. Relationships between on-treatment changes in indexes of left ventricular mass (LVM) and LV ejection fraction (EF) with LVM expressed as an inappropriate increase in LVM (LVM_{inappr}), absolute LVM or LVM indexed to height$^{2.7}$ (LVMI) in mild-to-moderate hypertension (n=168).

	Pearson's r (CI)	p value	Partial r (CI)	p value	Partial r (CI)	p value	Partial r (CI)	p value
Adjustments	None		confounders†		confounders†+EF_b		confounders†+ Δ LVM	
Change in ejection fraction versus								
Δ LVM_{inappr}	-0.29*(-0.42 to -0.14)	<0.0001	-0.38*(-0.50 to -0.23)	<0.0001	-0.35*(-0.48 to -0.21)	<0.0001	-0.63 (-0.71 to -0.52)	<0.0001
Δ LVM	0.08 (-0.07 to 0.23)	=0.30	0.17 (0.01 to 0.31)	=0.04	0.09 (-0.07 to 0.24)	=0.28	-	-
Δ LVMI	0.07 (-0.08 to 0.22)	=0.34	0.17 (0.01 to 0.32)	=0.04	0.10 (-0.06 to 0.25)	=0.22	-	-

A negative relationship represents an increase in EF with a decrease in LVM. CI, confidence interval; EF_b, baseline EF; Δ LVM, change in LVM. *p<0.0001 vs correlation coefficients for LVM and LVMI. †Adjustments are for age, sex, LV systolic stress, diabetes mellitus, pulse rate, previous treatment for hypertension, regular smoking, regular alcohol intake, body weight, body height (when assessing relations with LVM), and carvedilol therapy.

inverse relationships between change in or % change in LVM_{inappr} and change in or % change in EF were far stronger than the relationships between change in or % change in LVM or LVMI and change in or % change in EF (Table 5.8)($p<0.001$ for comparison of partial r values). The inverse relationship between change in LVM_{inappr} and change in EF remained unaltered despite further adjustments for change in LVM (Table 5.8) or change in LVMI (partial r=-0.64, confidence interval=-0.72 to -0.53, $p<0.0001$), baseline LVM (partial r=-0.42, confidence interval=-0.54 to -0.28, $p<0.0001$) or baseline LVMI (partial r=-0.42, confidence interval=-0.54 to -0.28, $p<0.0001$), change in stroke volume (partial r=-0.32, confidence intervals= -0.45 to -0.17, $p<0.0001$) or change in LV end diastolic diameter (partial r= -0.44, confidence intervals= -0.56 to -0.31, $p<0.0001$). The inverse relationship between % change in LVM_{inappr} and % change in EF also remained unaltered despite further adjustments for % change in LVM, or LVMI, baseline LVM or LVMI, % change in stroke volume or % change in LV end diastolic volume (data not shown). Replacing LV systolic wall stress with conventional, 24-hour, day, or night SBP showed similar relationships (data not shown).

5.3 Discussion

The main finding of the present study is that in the treatment of mild-to-moderate hypertension over a 4 month period, in contrast to a modest treatment-induced attenuation in EF accompanying decreases in LVM and LVMI, on-treatment decreases in LVM_{inappr} were strongly and independently related to improvements in EF. Importantly, relationships between on-treatment changes in LVM_{inappr} and EF were unaltered by adjustments for LVM or LVMI and were noted to be far stronger than relationships between on-treatment changes in LVM or LVMI and EF.

Although one prior study has demonstrated that on-treatment regression but not persistence of LVM_{inappr} is associated with an improved EF (Muiesan et al 2007), whether changes in EF associated with decreases in LVM_{inappr} are independent of or stronger than changes in LVM or LVMI is uncertain. To the best of my knowledge the present study

provides the first prospective, intervention data to show that regression of LVH as indexed by LVM_{inappr} is associated with improvements in EF beyond that of LVM or LVMI. The present study therefore supports the notion that LVH in excess of that predicted by stroke work, rather than absolute LVM, accounts for a decrease in LV systolic chamber function.

Prior studies showing inverse relationships between LVM_{inappr} and indices of systolic chamber 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, Muiesan et al 2007) have largely been reported in cross-sectional studies conducted in select clinical samples (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) and none have demonstrated these effects beyond LVM or LVMI. Such relationships may therefore reflect a compensatory increase in LVM in response to a depressed 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) to residual confounding effects (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, Muiesan et al 2007), or to an effect that is dependent on absolute LVM (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, Muiesan et al 2007). With respect to whether the relationships shown in the present study may also be attributed to a decrease in LVM in response to a reduction in LV systolic chamber function, there is little preclinical or clinical evidence to our knowledge to indicate that antihypertensive therapy is able to increase LV systolic chamber function independent of load over a short duration of therapy (4 months). In contrast, there is substantial evidence to show that antihypertensive therapy in-part regresses LVH over this time period. It is therefore likely that in the present study antihypertensive therapy regressed LVM_{inappr} and the reduced LVM_{inappr} or associated myocardial changes consequently enhanced EF.

Prior studies have demonstrated that regression of LVH following treatment with antihypertensive therapy is associated with either no change (Perlini et al 2001), or with

decreased (Wachtell et al 2002), rather than improved indices of systolic LV chamber function. Similarly, in the present study I show that decreases in LVM or LVMI are associated with a modest attenuation rather than an increase in EF with antihypertensive therapy. Together with the often enhanced EF observed relative to that predicted from LV wall stress in LVH (Hartford et al 1985), such data have previously cast doubt on inverse relationships between LVH and EF being attributed to LVH accounting for a decreased LV systolic chamber function. However, as in the present study on-treatment decreases in LVM_{inappr} were strongly and independently associated with the opposite effect on EF (an increase), the present study provides evidence to support the notion that LVH or factors related to LVH may be responsible for decreases in systolic LV chamber function, but that LVM_{inappr} and not absolute LVM or LVMI account for this effect.

Although not a primary outcome of the present study, it is important to consider the potential mechanisms for the on-treatment LVM_{inappr}-EF relations observed. In this regard EF is in-part determined by myocardial systolic function which is indexed by FSmid. Despite an ability to show strong inverse relations between FSmid and LVM_{inappr} independent of LVM or LVMI at baseline, following 4 months of antihypertensive therapy no significant relationships between change in FSmid and change in LVM_{inappr} were noted. These data suggest that on-treatment changes in FSmid over a short treatment period are too small to show relations with decreases in LVM_{inappr} unless larger study samples are employed. Indeed, prior studies have demonstrated that LVH regression following 3 months of antihypertensive treatment was associated with only a 0.6% increase in FSmid and required 152 patients to show a trend for significance (Perlini et al 2001).

The exact mechanisms at a myocardial level that may account for the improved LV systolic function associated with regression of an increased LVM_{inappr} are also unclear. This may reflect the regeneration of cardiomyocytes damaged by LVH-associated apoptosis and necrosis. However, the short duration over which LV systolic chamber function increased suggests an alternative mechanism, such as an improved cardiomyocyte function. In this regard, LVM_{inappr} may be accompanied by an imbalance in myocardial oxygen supply-to-

demand ratios, a change which promotes cardiomyocyte dysfunction. With a decrease in LVM_{inappr}, the balance between myocardial oxygen supply and demand may be restored and function improved.

Caution should be exercised when interpreting the results of the present study. In this regard, the present findings do not challenge the prognostic value of LVM or LVMI in contrast to LVM_{inappr}. Indeed, although not improving EF, antihypertensive therapy nevertheless also decreased LVM in participants with appropriate LVM and this is likely to be of prognostic importance. However, the present study does indicate that future prospective studies specifically assessing the impact of regression of increases in LVM_{inappr} independent of absolute LVM or LVMI on the development of heart failure with a reduced EF are required.

A limitation of the present study is that it was conducted in one ethnic group with a high prevalence of increased LVM_{inappr} and with higher thresholds for an increased LVM_{inappr} determined in a healthy sample, than that reported on in other ethnic groups. However, the thresholds for LVM_{inappr} corresponded to thresholds of LVMI of 51.8 $g/m^{2.7}$ in the healthy sample, an accepted threshold for LVMI in this ethnic group (Nunez et al 2005). An additional potential limitation is that I determined LVM_{inappr} using predicted LVM values calculated from a formula derived in an alternative population (de Simone et al 2002). However, in support of the suitability of the calculation of LVM_{inappr} in the patients studied, in contrast to strong positive correlations noted between LVM (or LVMI) and stroke work, when LVM was expressed as LVM_{inappr}, no residual relations with stroke work were observed. Moreover, the lack of ability to show reduced on-treatment decreases in BP and wall stress in response to antihypertensive therapy in the participants with an increased LVM_{inappr} as compared to those participants with an appropriate LVM, may reflect a type II statistical error. However, this is likely to have biased against the results of the present study and hence resulted in an underestimation of the size effect on EF that antihypertensive therapy could achieve in participants with an increased LVM_{inappr}. An additional limitation is that LV ejection fraction was measured with echocardiography whilst magnetic resonance imaging (MRI) measurements of systolic function have been demonstrated to be more sensitive for

predicting cardiovascular events (Mewton et al 2013). It is therefore possible that we may have demonstrated stronger relationships between change in LVMI and LV ejection fraction if magnetic resonance imaging had been employed. Last, relatively weak unadjusted correlation coefficients were noted for relationships between decreases in LVM_{inappr} and LV ejection fraction, a finding that must be interpreted with caution. This may reflect an overall weak relationship between change in LVH in excess of that predicted by stroke work and LV systolic chamber function. However, in multivariate models with adjustments for appropriate confounders and LVMI, we show a relationship (partial r value) between on-treatment change in LVM_{inappr} and increase in LV ejection fraction in mild-to-moderate hypertensives of -0.63 (confidence intervals=-0.71 to -0.52) ($p<0.0001$), a relationship which cannot be considered to be weak. Hence, it is likely that confounding effects explained the weak unadjusted relationships.

In conclusion, in the present study I show that with adjustments for LV wall stress and other confounders, in mild-to-moderate hypertension, treatment-induced decreases in LVM in excess of that predicted by LV work load (LVM_{inappr}) were strongly related to improvements in on-treatment EF independent of absolute LVM or LVMI. These data therefore support the notion that LVH, as indexed by LVM or LVMI incorporates a component of LVH that can be viewed as a compensatory change that preserves EF, but when this exceeds that predicted by LV workload, this excess in LV growth or associated changes, may account for decreases in EF. Future prospective studies specifically assessing the impact of regression of increases in LVM_{inappr} independent of absolute LVM or LVMI on the development of heart failure with a reduced EF are required.

CHAPTER 6

Independent Relationship Between Insulin Resistance and Inappropriate Left Ventricular Mass in a Community Sample with a High Prevalence of Obesity.

Abstract

An explanation for the relationship between obesity and left ventricular mass (LVM) in excess of that predicted from stroke work (inappropriate LVM [LVM_{inappr}]) and beyond alternative haemodynamic factors has not been provided. In the present study the relationship between the homeostasis model assessment of insulin resistance (HOMA-IR) and LVM_{inappr} beyond haemodynamic factors and adiposity indices was evaluated in 478 participants of a randomly selected community sample. 43% of the sample were obese and indices of adiposity were correlated with HOMA-IR ($p<0.0001$). With adjustments for confounders, waist circumference, but not body mass index was independently associated with HOMA-IR. HOMA-IR was correlated with LVM_{inappr} ($p<0.0001$) and in a multivariatre model with adjustments for waist circumference, age, sex, conventional systolic blood pressure, diabetes mellitus or an HbA1c>6.1%, regular tobacco use, regular alcohol intake, pulse rate, and treatment for hypertension, the relationship betwreen HOMA-IR and LVM_{inappr} persisted (partial $r=0.14$, $p<0.002$). With further adjustments for either 24-hour systolic BP (partial $r=0.11$, $p<0.05$, $n=351$), aortic pulse wave velocity (partial $r=0.13$, $p<0.02$, $n=410$), or circumferential LV wall stress (partial $r=0.12$, $p<0.02$, $n=478$) the independent relationship between HOMA-IR and LVM_{inappr} also remained. Multivariate adjusted LVM_{inappr} was markedly increased in the highest quartile as compared to the lowest quartile of HOMA-IR (131±28% vs 118±29%, $p<0.0005$). In conclusion, the present results suggest that independent of adiposity indices, insulin resistance is associated with LVM beyond that predicted from stroke work and independent of alternative haemodynamic changes. Hence, the relationship between indices of excess adiposity and LVM beyond haemodynamic factors may be explained in-part by insulin resistance.

6.0 Introduction

Left ventricular hypertrophy (LVH) is a predictor of heart failure (Casale et al 1986, Levy et al 1990, Ghali et al 1992, Levy et al 1996, Gottdiener et al 2000, Gardin et al 2001, Aurigemma et al 2001) and the development of a reduced ejection fraction (EF)(Drazner et al 2004) independent of myocardial infarction. Left ventricular mass (LVM) may therefore determine the progression to heart failure with a reduced rather than a preserved EF Drazner 2011, Bibbins-Domingo et al 2009). However, as highlighted in the previous two chapters of the present thesis, there are considerable discrepancies in the ability to show consistent relations between LVM or LVM index (LVMI) and a reduced systolic LV chamber function (Aurigemma et al 1995, de Simone[b] et al 1994, Shimizu et al 1991, Perlini et al 2001, Hartford et al 1985, Wachtell et al 2002). One possibility that may explain these inconsistencies is that absolute LVM and LVMI may incorporate a component of LVH considered compensatory in nature, whilst there may also be a component of LVH that contributes to decompensation. In this regard, LVM in excess of that predicted by work load (i.e. stroke work=blood pressure x stroke volume) termed “inappropriate LVM” (LVM_{inappr})(de Simone et al 1998), but not LVM or LVMI is inversely associated with systolic LV chamber function in an unselected community-based sample (Libhaber et al 2012) and on-treatment regression of LVM_{inappr}, but not LVM or LVMI is associated with an improved EF (Woodiwiss et al 2012). As highlighted in chapter 4, obesity is the strongest determinant of LVM_{inappr}. The mechanisms responsible for obesity-induced increases in LVM_{inappr} are nevertheless uncertain.

Although a number of studies with small sample sizes conducted in select patient populations (Sharp et al 1992, Sasson et al 1993, Lind et al 1995, Kamide et al 1996, Paolisso et al 1995, Paolisso et al 1997, Tomiyama et al 1997, Vetta et al 1998, Phillips et al 1998, Watanabe et al 1999, Shigematsu et al 2006, Anan et al 2007, Sesti et al 2007) and large study samples (Sundstrom et al 2008, Sciacqua et al 2011, Hwang et al 2011) have provided evidence to support a role for insulin resistance as a possible mechanism involved

in increasing LVM, these relationships could be accounted for by increases in stroke work associated with obesity. Indeed, one small study conducted in 53 hypertensives with electrocardiographic LVH from the LIFE study failed to demonstrate a irelationship between circulating insulin concentrations and LVM_{inappr} (Olsen et al 2004). The small study sample however raises the question of whether the results reflect a slection bias and a false negative relationship. Furthermore, in that study (Olsen et al 2004), insulin resistance was not determined. To address the question of whether insulin resistance is associated with LVM_{inappr}, in the present study I therefore evaluated whether an index of insulin resistance is associated with LVM_{inappr} independent of adiposity indices in a relatively large, randomly selected community-based sample with a high prevalence of obesity.

6.1 Methods

6.1.1 General

A description of the study sample has been provided in chapter 2 (pages 43-44). Of the 678 participants with echocardiographic data, fasting blood results were obtained from 478 participants. Demographic and clinical data were obtained using a standardised questionnaire described in chapter 2 (pages 44-45). Height and weight were measured using standard approaches and participants were identified as being overweight if their body mass index (BMI) was ≥25 kg/m^2 and obese if their BMI was ≥30 kg/m^2. Standard laboratory blood tests of renal function, liver function, blood glucose, lipid profiles, haematological parameters, and percentage glycated haemoglobin (HbA1c)(Roche Diagnostics, Mannheim, Germany) were performed. Fasting plasma insulin concentrations were determined from an insulin immulite, solid phase, two-site chemiluminescent immunometric assay (Diagnostic Products Corporation, Los Angeles, CA, USA) and insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the formula (insulin [uU/ml] x glucose [mmol/l])/22.5 (Wallace et al 2004). Diabetes mellitus (DM) or an abnormal

blood glucose control was defined as the use of insulin or oral hypoglycaemic agents or an HbA1c value greater than 6.1% (Bennett et al 2007). Menopause was confirmed with measurements of follicle stimulating hormone concentrations. Blood pressure (BP) measurements were obtained by a trained nurse-technician using a standard mercury sphygmomanometer and using SpaceLabs monitors (model 90207) (ambulatory 24-hour, day and night BP) as described in chapter 2, page 46. Carotid-femoral PWV was determined using applanation tonometry and SphygmoCor software as described in chapter 2, pages 46-47.

6.1.2 Echocardiography.

Echocardiography was performed as described in chapter 2, pages 47-55. All measurements were recorded and analyzed off-line by experienced investigators whom were unaware of the clinical data of the participants. Left ventricular mass (LVM), LVMI, and LV mean wall thickness were calculated as described in chapter 2, page 54. An LVMI >51 $g/m^{2.7}$ was considered to be increased (Nunez et al 2005). Stroke volume was evaluated from the difference between LV end diastolic and systolic volumes determined using both the Teichholz (Teichholz et al 1976) and the Z-derived (de Simone[c] et al 1996) methods. Circumferential LV systolic wall stress was calculated as described in chapter 4, page 95. The extent of inappropriate LVM (LVM_{inappr}) was determined from predicted LVM as described by others (de Simone et al 2002), where predicted LVM was calculated as $55.37+(6.64 \times height^{2.7})+(0.64 \times [systolic\ BP \times stroke\ volume \times 0.014]) - (18.07 \times gender)$, where male gender=1 and female gender=2, and where stroke volume was calculated from LV volumes assessed from the Z-derived method. Inappropriate LVM was expressed either as actual-predicted LVM in grams, or % actual LVM/predicted LVM. An $LVMI_{inappr}$>150% was considered to be increased. This threshold was identified from the upper 95% confidence interval for $LVMI_{inappr}$ determined in 140 participants from the community-based study without clinically significant disease and normal clinical blood parameters who were normotensive,

non-diabetic, and had a BMI<30 kg/m^2. In these participants the upper 95% confidence for LVMI was 51.8 g/$m^{2.7}$. To ensure that the calculation for LVM_{inappr} was suitable for the community studied, we determined whether the strong correlations between LVM or LVMI and stroke work were eliminated if LVM was expressed as LVM_{inappr}.

6.1.3 Data analysis

Database management and statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Continuous data are reported as mean±SD or mean±SEM. Unadjusted means and proportions were compared by the large-sample z-test and the χ^2-statistic, respectively. As HOMA-IR was positively skewed (see page 76 for skewness, kurtosis and Shapiro-Wilk's statistic) HOMA-IR was log transformed (see page 76 for skewness, kurtosis and Shapiro-Wilk's statistic after log transformation) Independent relations between HOMA-IR and LVM, LVMI or LVM_{inappr} were determined from multivariate linear regression analysis with adjustments for waist circumference, age, sex, conventional systolic BP (or 24-hour systolic BP, PWV or circumferential wall stress), diabetes mellitus or an HbA1c>6.1%, antihypertensive treatment, regular tobacco use and regular alcohol intake. Partial correlation coefficients between HOMA-IR and LVM, LVMI or LVM_{inappr} were determined by assessing these relations after adjusting for covariates. Probability values were further adjusted for non-independence of family members using the method of maximum likelihood as implemented by the mixed procedure as defined in the SAS package. The mixed model contains both fixed effects (all phenotypic data) parameters and random-effects (familial relationships) parameters. To compare the magnitude of the impact of different variables on LVM, LVMI and LVM_{inappr}, standardized β-coefficients were determined from stepwise linear regression analysis and these coefficients compared using a one way analysis of variance.

6.2 Results

6.2.1 Participant characteristics.

The demographic and clinical characteristics of participants with echocardiographic data either with or without fasting blood data were similar (see Table 3.1 for comparison). A high proportion of participants were overweight or obese (Table 3.1). Of the 42.1% of participants that were hypertensive, only 38.3% had controlled BP. 23.2% of participants had LVH (LVMI>51 g/$m^{2.7}$). Approximately a quarter of the participants had diabetes mellitus or an impaired blood glucose control. None of the participants had mitral valve abnormalities. 15.5% of participants had an increased LVM_{inappr}. The mean (±SD) HOMA-IR and log HOMA-IR values in those with fasting blood values were 3.70±5.14 and 0.70±1.09 respectively.

6.2.2 Factors related to HOMA-IR.

On bivariate analysis, the factors related to HOMA-IR have been described in section 3.2.2 (chapter 3). In a multivariate regression model, only waist circumference and diabetes mellitus and/or an HbA1c>6.1% were independently associated with HOMA-IR (see Table 3.3 of chapter 3).

6.2.3 Relationships between indices of excess adiposity and LVM_{inappr}.

The relationships between indices of excess adiposity and LVM_{inappr} are shown in Figure 4.1 (chapter 4). The multivariate adjusted relationships between indices of excess adiposity and LVM_{inappr} are shown in Tables 4.3 and 4.4 (chapter 4).

6.2.4 HOMA-IR is independently associated with an inappropriate left ventricular mass

On bivariate analysis, HOMA-IR was strongly and directly correlated with LVM, LVMI and LVM_{inappr} (Figure 6.1). In multivariate models with waist circumference, age, sex, conventional systolic BP, diabetes mellitus or an HbA1c>6.1%, regular tobacco use, regular alcohol intake, and treatment for hypertension in the model, HOMA-IR was independently associated with LVM, LVMI and LV_{inappr} (Figure 6.2). With further adjustments for body weight (LVMI) or body mass index (LVM and LVM_{inappr}) in place of waist circumference in the multivariate models, HOMA-IR remained independently related to LVM (partial r=0.16, p=0.0006), LVMI (partial r=0.12, p=0.008) and LVM_{inappr} (partial r=0.16, p<0.0005). An incremental increase in multivariate adjusted LVM_{inappr} was noted across quartiles of log HOMA-IR (Figure 6.3).

6.2.5 Relationship between HOMA-IR and inappropriate left ventricular mass beyond additional haemodynamic factors.

With adjustments for 24-hour systolic BP, circumferential wall stress or aortic PWV in place of conventional systolic BP in the multivariate models, HOMA-IR remained independently related to LVM, LVMI and LVM_{inappr} (Table 6.1).

6.3 Discussion

The main findings of the present study are that in a randomly selected community sample with a high prevalence of obesity, insulin resistance as indexed by HOMA-IR, was associated with LVM in excess of that predicted by stroke work (LVM_{inappr}) independent of indices of excess adiposity including general (BMI) and central (abdominal) (waist circumference) adiposity and of a number of haemodynamic factors including circumferential wall stress, 24-hour BP and aortic PWV.

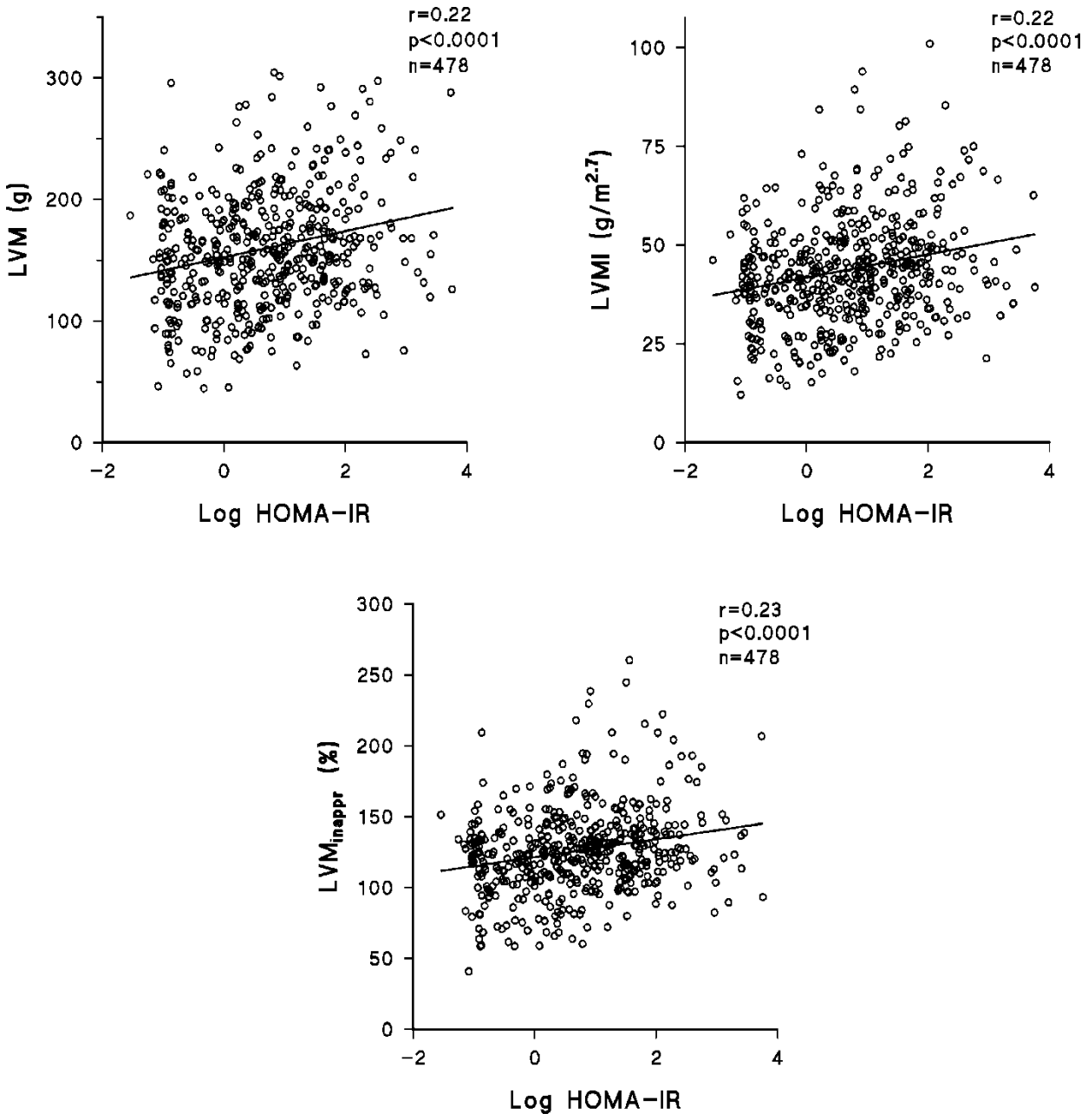


Figure 6.1. Bivariate relationship between the log of the homeostasis model assesment of insulin resistance (HOMA-IR) and left ventricular mass (LVM), LVM index (LVMI) and LVM in excess of that predicted by stroke work (inappropriate LVM, LVM_{inappr}) in a community sample.

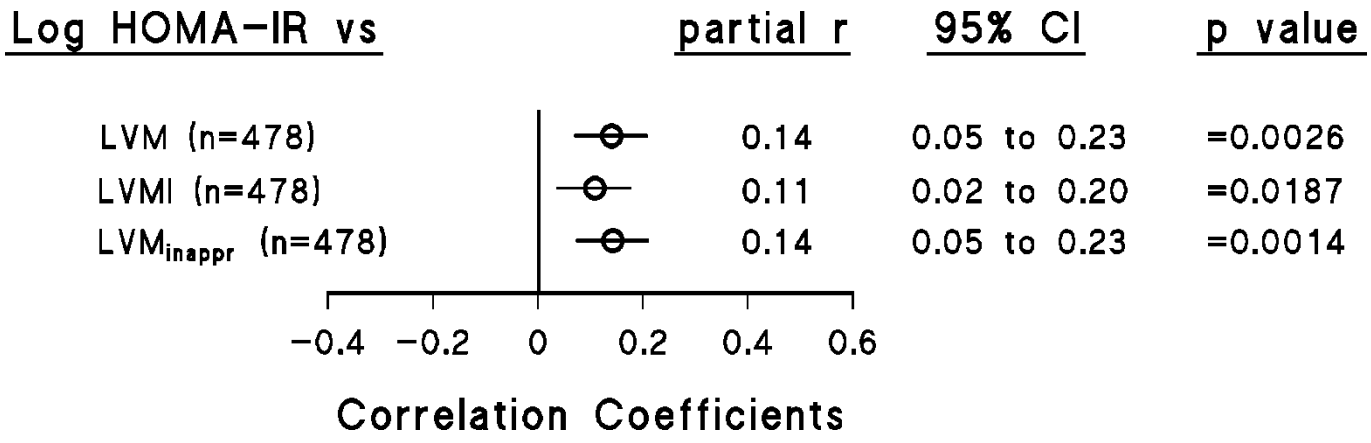


Figure 6.2. Partial correlations coefficients and 95% confidence intervals of the multivariate adjusted relationships between the log of the homeostasis model assesment of insulin resistance (HOMA-IR) and left ventricular mass (LVM), LVM index (LVM) or LVM in excess of that predicted by stroke work (inappropriate LVM, LVM_{inappr}) in a community sample. Adjustments were for age, sex, waist circumference, conventional systolic BP, diabetes mellitus or a glycated hemoglobin>6.1%, antihypertensive treatment, regular tobacco use and regular alcohol intake. Probability values were further adjusted for non-independence of family members.

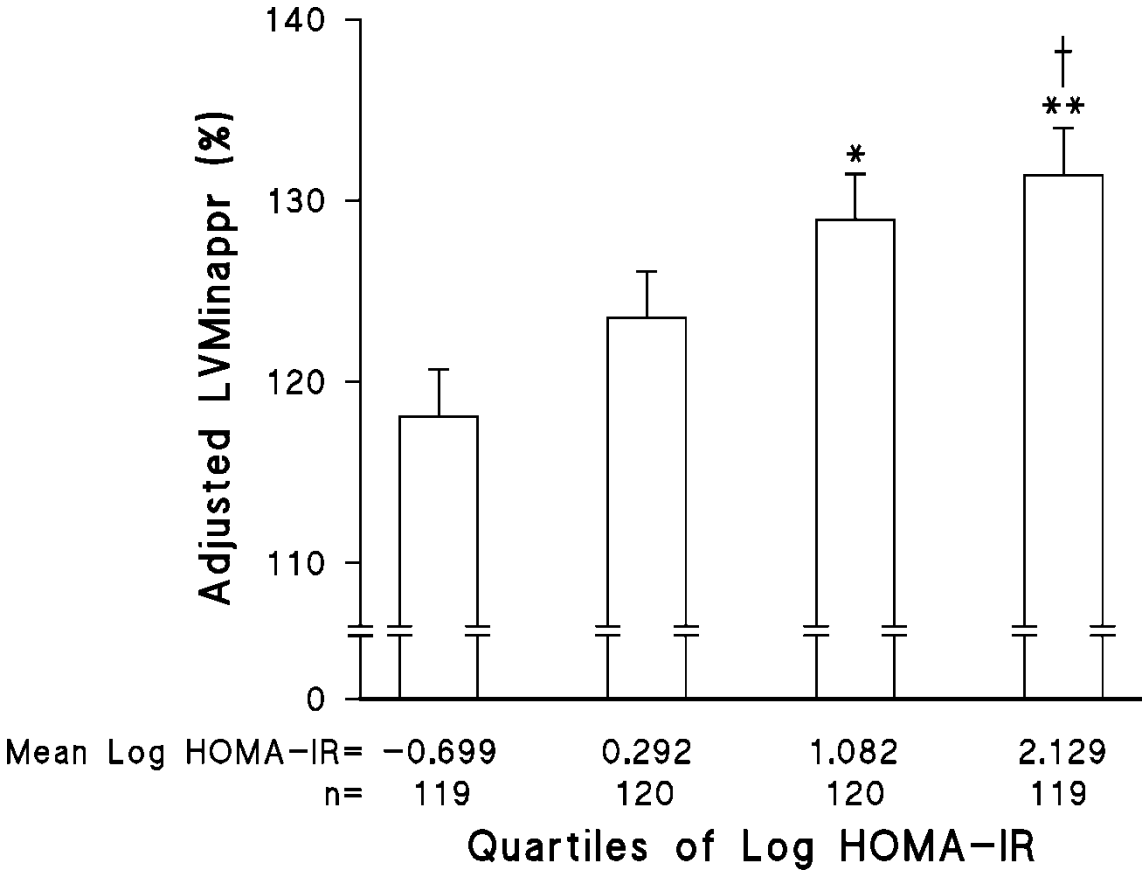


Figure 6.3. Multivariate adjusted left ventricular mass (LVM) in excess of that predicted by stroke work (inappropriate LVM [LVM_{inappr}]) across quartiles of the log of the homeostasis model assesment of insulin resistance (HOMA-IR) in a community sample. Adjustments were for age, sex, waist circumference, systolic blood pressure, diabetes mellitus or a glycated hemoglobin>6.1%, antihypertensive treatment, regular tobacco use, and regular alcohol intake. Probability values were further adjusted for non-independence of family members. *p<0.005, ** p<0.0005 vs first quartile, †p<0.05 versus second quartile of HOMA-IR.

Table 6.1. Independent relationships between the log of the homeostasis model assesment of insulin resistance (HOMA-IR) and left ventricular mass (LVM), LVM index (LVM) or LVM in excess of that predicted by stroke work (inappropriate LVM, LVM_{inappr}) in a community sample with adjustments for potential confounders and various haemodynamic factors.

HOMA-IR vs	n=	Adjustments	Partial r	Confidence intervals	p-value
LVM	351	* + 24-hour SBP	0.12	0.014 to 0.225	<0.05
	410	* + Aortic PWV	0.14	0.038 to 0.231	<0.01
	478	* + Circ. wall stress	0.13	0.036 to 0.216	<0.01
LVMI	351	* + 24-hour SBP	0.11	0.001 to 0.211	<0.05
	410	* + Aortic PWV	0.10	0.001 to 0.211	<0.05
	478	* + Circ. wall stress	0.10	0.001 to 0.186	<0.05
LVM_{inappr}	351	* + 24-hour SBP	0.11	0.001 to 0.211	<0.05
	410	* + Aortic PWV	0.13	0.030 to 0.224	=0.01
	478	* + Circ. wall stress	0.12	0.029 to 0.210	=0.01

SBP, systolic blood pressure; PWV, pulse wave velocity; Circ, circumferential. *Adjustments are for age, sex, waist circumference, diabetes mellitus or a glycated hemoglobin>6.1%, antihypertensive treatment, regular tobacco use and regular alcohol intake and haemodynamic factor as indicated. Probability values were further adjusted for non-independence of family members.

To the best of my knowledge the present study is the first to show that insulin resistance is associated with LVM independent of adiposity indices and beyond that produced by stroke work (the major haemodynamic factor that determines variations in LVM) and a number of alternative haemodynamic factors including circumferential wall stress, 24-hour BP and aortic PWV. The present study is therefore the first to show that the relationship between insulin resistance and LVM may be accounted for by non-haemodynamic effects. In this regard, although a number of both small studies conducted in select clinical samples (Sharp et al 1992, Sasson et al 1993, Lind et al 1995, Kamide et al 1996, Paolisso et al 1995, Paolisso et al 1997, Tomiyama et al 1997, Vetta et al 1998, Phillips et al 1998, Watanabe et al 1999, Shigematsu et al 2006, Anan et al 2007, Sesti et al 2007) and large studies (Sundstrom et al 2008, Sciacqua et al 2011, Hwang et al 2012) have demonstrated that insulin resistance may account for variations in LVM, these effects may be attributed entirely to the well described haemodynamic effects of obesity including increases in 24-hour BP, stroke volume, preload, or aortic PWV, none of which were adjusted for in these prior studies. Furthermore, in two of the large studies (Sundstrom et al 2008, Hwang et al 2012), the relationships between indices of insulin resistance and LVM were not adjusted for indices of excess adiposity, whilst in the present study the relations between HOMA-IR and LVM persisted with adjustments for an index of either abdominal obesity (waist circumference) or for body size (BMI or body weight).

In contrast to the present and prior studies showing relations between indices of insulin resistance and LVM beyond those of adiposity indices (Sharp et al 1992, Sasson et al 1993, Lind et al 1995, Kamide et al 1996, Paolisso et al 1995, Paolisso et al 1997, Tomiyama et al 1997, Vetta et al 1998, Phillips et al 1998, Watanabe et al 1999, Shigematsu et al 2006, Anan et al 2007, Sesti et al 2007, Sundstrom et al 2008, Sciacqua et al 2011, Hwang et al 2012), a number of small studies conducted in select clinical samples (Nagano et al 1994, Kupari et al 1994, Costa et al 1995, Ohya et al 1996, Muredda et al 1998, Jelenc et al 1998, Verdecchia et al 1999, Galvan et al 2000, Malmquist et al 2001, Olsen et al 2003, Ebnic et al 2006) or in large study samples (Chen et al 1998, Sundstrom et al 2000,

Devereux et al 2002, Rutter et al 2003, Velagaletti et al 2010, Fox et al 2011, de Simone et al 2003, 2011) have failed to demonstrate a relationship between indices of insulin resistance and LVM independent of adiposity indices or BP.

In this regard an inability to show a relationship in small studies conducted in select clinical samples (Nagano et al 1994, Kupari et al 1994, Costa et al 1995, Ohya et al 1996, Merudda et al 1998, Jelenc et al 1998, Verdecchia et al 1999, Galvan et al 2000, Malmquist et al 2001, Olsen et al 2003, Ebnic et al 2006) may be attributed to a selection bias or to a false negative finding. In contrast, in the present study I show relations between HOMA-IR and LVM in an unselected and relatively large community-based sample. An inability to show independent relations between indices of insulin resistance in previous large clinical samples may also be attributed in-part to differences in the indices of insulin resistance employed in these studies. In this regard, whilst in the present study I assessed HOMA-IR as an index of insulin resistance, a measurement which mirrors the outcomes of the more sensitive glucose clamp technique (Bonara et al 2000), some previous large studies have evaluated relationships between C-peptide (Chen et al 1998) or circulating insulin concentrations (Devereux et al 2002). Moreover, differences in the characteristics of the populations studied may explain apparent discrepancies in results between strudies. In this regard, insulin resistance as assessed from the euglycaemic insulin clamp technique, was not independently associated with LVMI in elderly men (Sundstrom et al 2000), whilst the present study was conducted in a randomly selected community sample. However, in both the present and a number of alternative studies (Rutter et al 2003, Velagaletti et al 2010, Fox et al 2011, de Simone et al 2003, 2011) showing a lack of relationship between insulin resistance and LVM, HOMA-IR was employed to assess insulin resistance and the populations or communities sampled were randomly selected. Nevertheless, colinearity between HOMA-IR and indices of excess adiposity may have abolished relationships between HOMA-IR and LVM once adjustments for adiposity indices were applied in these studies (Rutter et al 2003, Velagaletti et al 2010, Fox et al 2011, de Simone et al 2003, 2011). In addition, in none of these prior studies (Rutter et al 2003, Velagaletti et al 2010,

Fox et al 2011, de Simone et al 2003, 2011) was the relationship between HOMA-IR and LVM_{inappr} assessed.

Although speculative in nature, the clinical implications of the present study warrant consideration. If the relationship between HOMA-IR and LVM_{inappr} is confirmed in longitudinal studies, the results of the present study suggest that insulin resistance may in-part contribute toward the development of LVM_{inappr} and in view of the potential role of LVM_{inappr} as a possible cause of a reduced left ventricular ejection fraction (see preceding 2 chapters), improving insulin resistance even in the absence of overt diabetes mellitus may play a significant role in reducing the development of heart failure with systolic dysfunction. The notion that insulin resistance may lead to left ventricular systolic dysfunction is consistent with recent evidence of impaired contractile reserve in insulin resistant subjects (Cadeddu et al 2013). An intervention study is warranted to provide proof-of-principle that therapeutic agents that improve insulin resistance can regress excess LVM_{inappr} and in the absence of overt diabetes mellitus, improve left ventricular systolic function.

The limitations of the present study are largely those acknowledged in preceding chapters of the present thesis. The present study was a cross-sectional design and hence does not allow for conclusions to be drawn regarding cause and effect. Second, the present study was conducted in one ethnic group (black African descent) with a high prevalence of LVM_{inappr} and with higher thresholds for an increased LVM_{inappr} determined in a healthy sample, than that previously reported on in other ethnic groups. However, the thresholds for LVM_{inappr} corresponded to thresholds of LVMI of 51.8 $g/m^{2.7}$ in the healthy sample, an accepted threshold for LVMI in this ethnic group (Nunez et al 2005). Third, I determined LVM_{inappr} using predicted LVM values calculated from a formula derived in an alternative population (de Simone et al 2002). However, in support of the suitability of the calculation of LVM_{inappr} in the community studied, in contrast to strong positive correlations noted between LVM (or LVMI) and stroke work, when LVM was expressed as LVM_{inappr}, no residual relations with stroke work were observed. Last, relatively weak partial r values were noted for relationships between HOMA-IR and LVM_{inappr}, a finding that must be interpreted with

caution. This may reflect an overall weak relationship between insulin resistance and LVM_{inappr}; an inability to appropriately account for all confounders or to exclude the impact of co-linearity between adjustors in multivariate models; or to our inability to accurately identify the degree of insulin resistance using for example a euglycaemic insulin clamp. However, this relationship translated into a more than 10% difference in LVM_{inappr} between the highest and lowest quartile of HOMA-IR, a size effect that cannot be considered as trivial. Only intervention studies targeting insulin resistance are likely to reveal the actual magnitude of the effect of insulin resistance on LVM_{inappr} if indeed this relationship is cause and effect.

In conclusion, in the present study I show that insulin resistance, as indexed by HOMA-IR is associated with LVM in excess of that predicted by workload independent of adiposity indices as well as a number of additional haemodynamic changes including 24-hour BP, circumferential wall stress and aortic PWV. These results therefore provide evidence to support a non-haemodynamic effect of insulin resistance on LVM and in-part explain the strong and independent relationship between obesity and LVM in excess of that predicted by workload.

CHAPTER 7

Summary and conclusions.

As discussed in chapter 1 there is now considerable data to show that the presence of overweight or obesity contributes toward the development of heart failure independent of a number of conventional cardiovascular risk factors as well as the presence of myocardial infarction (Chen et al 1999, He et al 2001, Johansson et al 2001, Wilhelmsen et al 2001, Kenchaiah et al 2002, 2009, Ingelsson et al 2005a and 2005b, Nicklas et al 2006, Bahrami et al 2008, Spies et al 2009). Although there is no question that successful weight reduction or prevention programmes are the ultimate solution to this problem, unfortunately weight reduction programmes seldom result in obese individuals reaching target body weights (Latner et al 2002, Anderson et al 2001) and often result in an ability to maintain decreases in body weight (Jordan et al 2012, Hedayati et al 2011, Aucott et al 2009, Weiss et al 2007, The Trials of Hypertension Prevention Collaborative Research Group 1997). In this regard adherence to lifestyle changes decrease from as early as 6 months after the initiation of weight reduction programmes (Elmer et al 2006). Thus, it may be necessary to introduce alternative approaches to prevent the transition from overweight and obesity to heart failure. In order to institute effective therapeutic strategies, a complete understanding of the mechanisms of obesity-associated cardiovascular risk is necessary. However, as also undesrcored in previous chapters of the present thesis, the exact mechanisms responsible for this effect and the pathophysiological processes are unclear. These uncertainties prompted me to conduct a number of studies that have ultimately contributed toward these fields of study.

In the present thesis I have produced evidence that contributes toward our understanding of the pathophysiological processes responsible for the transition from obesity-associated LVH to cardiac decompensation and some insights into the mechanisms that may explain these effects. In the present chapter I will discuss these findings in the context of some of the outstanding controversies which existed in this regard, and I will advance possible solutions based on the findings in the present thesis for preventing the problem of obesity-associated heart failure. Consistent with the general themes followed in the present thesis I will discuss these issues under two broad headings related to the two

main pathophysiological mechanisms known to contribute toward heart failure, namely "diastolic" and "systolic" cardiac dysfunction. However, initially I will discuss the strengths and weaknesses of the study design employed in the present thesis as it is important to place the findings of the current thesis in the context of these strengths and weaknesses.

7.1 Study designs that could be employed to evaluate the process involved in the transition from obesity-associated LVH to heart failure.

It is important to consider that with respect to the question of the role of obesity as a possible contributing factor to the development of cardiac dysfunction, I performed a relatively large cross-sectional, community-based study with random selection procedures conducted in a population with a high prevalence of obesity. The strengths of such a study are the fact that the results are unlikely to represent false positive or false negative findings or the effects of a selection bias so frequently encountered in case-control studies. The weaknesses of the present study are the inability to draw conclusions regarding cause and effect and the fact that hard outcomes of clinical significance were not evaluated. In this regard, a longitudinal study designed to evaluate whether overweight and obesity predicts the development of heart failure with either LV systolic or diastolic dysfunction independent of traditional cardiovascular risk factors or coronary artery disease would provide a high level of evidence in favour of the pathophysiological process involved in obesity-associated heart failure. However, with respect to such a study design there are a number of issues that require consideration.

It is likely that well before the development of symptoms or signs of heart failure, at least one of the traditional risk factors for heart failure would occur in patients whom are overweight or obese. Thus, a longitudinal study is always likely to be confounded by the fact that obesity is associated with the development of hypertension, diabetes mellitus, dyslipidaemia and coronary artery disease, all of which may contribute toward the development of LV systolic or diastolic dysfunction and ultimately heart failure. Hence, the

chances of residual confounding effects are high. In contrast, in a cross-sectional study the impact of overweight or obesity on early as opposed to late LV dysfunction may be detected, changes which may frequently precede the development of traditional risk factors. Thus, although residual confounding effects cannot be eliminated in a cross-sectional study, they at least can be limited by seeking early LV dysfunction. Furthermore, an outcome-driven study may be confounded by decreases in body weight which are often associated with the development of heart failure (cardiac cachexia). In contrast, in a cross-sectional study, the chances that cardiac cachexia may confound the results would obviously be markedly reduced. A longitudinal study would also require considerable resources and time for follow-up and may ultimately lead to data emerging at a point in time that may be considered as too late to rectify the current problems associated with emerging epidemics of obesity world-wide. In contrast, cross-sectional studies may be conducted over shorter time periods. In the context of the strengths and weakness of the study designs, the work conducted in the present thesis nevertheless provides a number of insights into the pathophysiological process involved in the transition to heart failure associated with overweight or obesity. What are these insights?

7.2 The transition from obesity-associated LVH to *diastolic* LV dysfunction.

As indicated in chapter 1 and again briefly highlighted in the introduction to chapters 2 and 3, prior to the publication or presentation of the data obtained in the present thesis, there were a number of unresolved issues with respect to the role of overweight and obesity as factors that may play a role in the pathogenesis of LV diastolic dysfunction. In the following I will discuss the results of the present thesis in the context of of each of these unresolved issues. In this way the contribution and the importance of the data obtained in the present thesis will be underscored. I will also suggest further studies required to address either the limitations of the data obtained in the present thesis or that will further evaluate the hypotheses that have been generated by the present thesis.

7.2.1 Does obesity contribute to variations in LV diastolic dysfunction at a population or community level?

In the present thesis I was able to show that independent of a number of confounders, waist circumference, or BMI were inversely associated with E/A and e'/a' in a relatively large, randomly selected, community based adult sample. It is important to underscore first that echocardiographic measures of LV diastolic dysfunction as determined from transmitral velocity measurements (E/A) and tissue Doppler assessments (E/e') are associated with adverse cardiovascular outcomes and the development of heart failure (Aurigemma et al 2001, Schillaci et al 2002, Bella et al 2002, Redfield et al 2003, Ammar et al 2008). Hence, the extent to which excess adiposity explains variations in LV diastolic function has potential clinical importance. In this regard, until recently it was uncertain to what extent overweight and obesity contributed toward variations in LV diastolic function at a population or community level. What were the limitations of prior evidence and how has the present thesis contributed toward our understanding of this field? Importantly, I will not contrast the evidence obtained in the present study with case-control studies where the possibility of a selection bias or false positive or false negative findings are high. Rather, I will restrict the comparisons to data obtained only in large, randomly selected studies where false positive or false negative findings are limited and a selection bias is restricted to the criteria employed for random selection.

Although prior studies conducted in large, randomly selected study samples have demonstrated an independent relationship between indices of excess adiposity and abnormalities of diastolic function (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003, Tsioufis et al 2009, Russo et al 2011), these relationships were either not adjusted for confounders (Redfield et al 2003); were modest at best (Redfield et al 2003, Fischer et al 2003); were conducted in hypertensives only (Tsioufis et al 2009) where the residual confounding effects of hypertension cannot be eliminated; were conducted in a population

sample of middle-aged-to-elderly individuals only (Redfield et al 2003, Ammar et al 2008) where the residual confounding effects of age on diastolic function cannot be eliminated; were not adjusted for LVMI or relative wall thickness (Redfield et al 2003, Ammar et al 2008; Tsioufis et al 2009); or were published after (Russo et al 2011) the results of the present study (Libhaber et al 2009). Thus, to the best of my knowledge, the results of the present thesis are the first to provide a reflection of the independent impact of excess adiposity on LV diastolic function in an unselected community-based sample not limited by a selection bias.

In contrast, also at the time that the first paper related to the present thesis was published (Libhaber et al 2009), some studies had failed to establish a contribution (Bella et al 2002, Chinali et al 2006) and others had demonstrated a relatively minor contribution (Fischer et al 2003) of obesity to LV diastolic function. There are a number of potential explanations for the lack of or minimal relationships noted in these studies. The lack of independent relationship between adiposity and E/A in adolescents (Chinali et al 2006) may relate to the younger age of the participants as compared to other studies. Nevertheless, the presence of an abnormal E/A in adult participants with a reduced as opposed to increased BMI is difficult to explain (Bella et al 2002) unless differences in loading conditions influenced the outcome of this study. An alternative explanation is that differences in the anthropometric measures employed to index obesity, where measures of central adiposity may be more closely associated with abnormalities of LV diastolic chamber function than BMI (Ammar et al 2008, Tsioufis et al 2009), could explain discrepancies between studies. Indeed, in studies that failed to show a relationship or showed only a modest relationship between adiposity indices and LV diastolic function (Bella et al 2002, Chinali et al 2006, Fischer et al 2003), only BMI was employed as an index of excess adiposity. In this regard, in agreement with prior studies that have demonstrated a less robust relationship between BMI and abnormalities of diastolic function (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003) as compared to that between indices of central adiposity and abnormalities of diastolic function (Ammar et al 2008, Tsioufis et al 2009), in the present study no significant

independent relationship between BMI and E/A was noted after adjustments for waist circumference, despite persistence of the independent relationship between an index of central adiposity (waist circumference) and E/A after adjustments for alternative indices of adiposity (BMI and skinfold thickness). However, at variance to a previous study (Ammar et al 2008), in the present study I failed to show an independent relationship between waist-to-hip ratio and E/A. Although an explanation for the differences between studies is not apparent, such disparities could be attributed to distinct characteristics of the study populations.

The results of the present thesis also provide the first indication of the extent to which indices of excess adiposity may explain variations in LV diastolic function in comparison to the contribution of other factors well established as determinants of LV diastolic function. In this regard, the results of the present study indicate that at a community level, waist circumference is second only to age and equivalent to BP in the magnitude of the effect on E/A. Although prior to the publication of the present study (Libhaber et al 2009), an alternative study performed in the general population had reported on independent associations between indices of central obesity and abnormalities of LV diastolic function (Ammar et al 2008), the relative impact of central adiposity on E/A as compared to alternative cardiovascular risk factors, was unclear.

7.2.2 Do haemodyamic factors contribute toward obesity-associated decreases in LV diastolic dyfsunction?

Although some large community- or population-based studies have reported on an independent relationship between adiposity indices and abnormalities of LV diastolic function either prior to (Redfield et al 2003, Ammar et al 2008, Fischer et al 2003, Tsioufis et al 2009) or after (Russo et al 2011) publication of the work contained within the present thesis (Libhaber et al 2009), none of these studies had considered all potential haemodynamic factors involved. In this regard, a number of studies have demonstrated that obesity is

associated with increases in arterial stiffness (Sutton-Tyrrell et al 2001, Mackey et al 2002, Wildman et al 2003, Majane et al 2008), and indices of arterial stiffness are associated with LVMI independent of brachial BP (Libhaber et al 2008). As LVMI may be an important determinant of LV diastolic function (Fischer et al 2003, Chahal et al 2010, Schillaci et al 2002), the role of obesity-associated increases in artrial stiffness therefore requires careful consideratiion. Moreover, prior studies reporting on the independent relationship between adiposity indices and LV diastolic function have only adjusted for office BP, and had not considered the possibility that obesity-associated increases in 24-hour BP may explain the independent relationships between excess adiposity and LV diastolic dysfunction. However, in the present thesis I was able to show that waist circumference was associated with E/A even after adjustments for aortic pulse wave velocity, an index of large artery stiffness, or 24-hour BP. Thus, the present thesis provides the only evidence to support the notion that obesity is associated with LV diastolic dysfunction even beyond not only office BP, or hyperternsion status, but also beyond aortic stiffness and 24-hour BP. The clinical implications of these findings are that targeting obesity-associated haemodynamic changes is unlikely to prevent or improve LV diastolic dysfunction.

7.2.3 Does obesity contribute to variations in LV diastolic dysfunction independent of left ventricular hypertrophy or remodelling?

As indicated throughout the thesis, LVMI and concentric LV remodelling are strongly associated with LV diastolic dysfunction (Fischer et al 2003, Chahal et al 2010, Schillaci et al 2002). An obvious question which therefore arises is whether obesity-associated LVH is an essential element involved in the transition to an abnormal LV diastolic function? In this regard, prior to the initial publication of the work contained within the present thesis (Libhaber et al 2009), independent associations between indices of central obesity and abnormalities of LV diastolic function previously reported on in most large studies conducted at a population or community level were not adjusted for either LVMI or LV relative wall

thickness (Redfield et al 2003, Ammar et al 2008, Tsioufis et al 2009), whilst adjustments for LVMI or relative wall thickness in other studies resulted in only marginal associations between obesity and LV diastolic function (Fischer et al 2003). In the present study I was able to show that the strength of the independent relations between indices of adiposity and E/A were retained after adjustments for either LVMI or LV relative wall thickness. To the best of my knowledge therefore, the present study was the first relatively large study conducted at a community level to suggest that LVM and geometry may contribute only to a minor extent to the pathogenesis of obesity-induced LV diastolic abnormalities. Although subsequent larger studies have similarly demonstrated relations between excess adiposity and diastolic dysfunction independent of LVMI (Russo et al 2011), this study did not report on adjustments for relative wall thickness. However, as obesity was not associated with an increased relative wall thickness in that study (Russo et al 2011), both the present (published in 2009, Libhaber et al 2009) and this prior (Russo et al 2011) study are consistent with each other. Overall therefore, the current evidence supports a view that LVH or concentric LV remodelling are not prerequisites for the transition to LV diastolic dysfunction associated with overweight or obesity. The clinical implications of these findings are that targeting LVH or the concentric LV remodelling process is unlikely to prevent or improve LV diastolic dysfunction associated with overweight or obesity. What then is the mechanism that may explain the LV diastolic dyfsunction in obesity?

7.2.4 Insulin resistance as a possible explanation for the association between adiposity indices and LV diastolic dysfunction.

As insulin resistance, an often noted finding associated with obesity, may either downregulate myocardial glucose uptake, thus precluding the energetic advantage provided by glucose versus free fatty acid oxidation, or result in an accumulation of intracellular triacylglycerol, thus promoting lipotoxicity (Nikolaidis et al 2004, Ouwens et al 2005, Coort et al 2007), in the present thesis I considered the possibility that insulin resistance may explain

the independent relationships between adiposity indices and LV diastolic dysfunction. In this regard, prior to the present thesis, several studies conducted in select clinical samples and with small or relatively small study sizes (Lind et al 1995, Golderisi et al 1997, Mureddu et al 1998, Watanabe et al 1999, Wong et al 2004, Bajraktari et al 2006, Dinh et al 2010 Utz et al 2011, Sliem et al 2010), or in large study samples (Hwang et al 2011) had suggested that insulin resistance is associated with abnormalities in LV diastolic function. However, in one study these relationships were not independent of adiposity indices (Mureddu et al 1998) and in other studies (Lind et al 1995, Golderisi et al 1997, Mureddu et al 1998, Watanabe et al 1999, Wong et al 2004, Dinh et al 2010 Utz et al 2011, Sliem et al 2010) including the study with a large study sample (Hwang et al 2011) these relationships were either not adjusted for adiposity indices or indices or central (abdominal) adiposity. Moreover, it is uncertain whether these relationships could be accounted for by haemodynamic changes other than clinic BP, including 24-hour BP and aortic stiffness.

In contrast to studies showing obesity-LV diastolic function relations, in alternative small studies (Olsen et al 2003, Wada et al 2010, Wu et al 2011, Lambert et al 2010) also conducted in select clinical samples, indices of insulin resistance were not correlated with measures of diastolic function. However, as demonstrated in chapter 3 of the present thesis, in a study design which precludes the possibility of a potential selection bias, or type I or II statistical errors, I was able to demonstrate that HOMA-IR, an index of insulin resistance, was associated with LV diastolic function independent of adiposity indices or haemodynamic changes, including aortic PWV and 24-hour BP. Moreover, although independent relationships between HOMA-IR and LVMI or relative wall thickness were noted, adjustments for LVMI nor relative wall thickness modified the multivariate adjusted HOMA-IR-E/A relationships. These data would therefore suggest that LV structural changes are unlikely to account for relationships between HOMA-IR and abnormalities of LV diastolic function. With respect to the clinical implications of this finding, one must therefore consider insulin resistance as a potential mechanism mediating LV diastolic dysfunction in obesity. Taking this argument one step further, it is possible therefore that insulin resistance may

contribute toward the transition to heart failure in obesity. What are the possible questions raised by these findings with respect to future studies?

7.2.5 Obesity and insulin resistance may contribute toward variations in LV diastolic dysfunction: Future directions.

Considering that the world currently faces the challenge of an epidemic of obesity and its potential consequences, the results of chapter 2 and 3 presented in the current thesis require careful consideration. Without question the reults presented in chapters 2 ahd 3 raise the question of whether in the absence of diabetes mellitus, obesity, through insulin resistance may present a risk factor for heart failure through a decrease in diastolic LV function. The present thesis therefore raises the question of whether we wait for longitudinal studies with hard outcomes to confirm the present results, studies which would undoubtedly lend more scientific rigor to the question, or whether we begin small “proof-of-principle” studies to evaluate the possibility that targeting insulin resistance may improve diastolic LV function. The dilemma obviously requires consideration within the context of a potential epidemic of obesity associated heart failure. In this regard, I am aware of a number of laboratories world-wide that have earmarked on either one or the other study design. If successful, these studies would ultimately lend credence to the possibility that insulin sensitising agents in those whom are unable to modify insulin resistance with interventions designed to achieve weight loss, may be a solution to preventing obesity-associated LV diastolic LV dysfunction and hence heart failure.

7.3 The transition from obesity-associated LVH to *systolic* LV dysfunction.

As indicated in chapter 1 and again briefly highlighted in the introduction to subsequent chapters, prior to the publication or presentation of the data obtained in the present thesis, there were also a number of unresolved issues with respect to the role of

overweight and obesity as factors that may play a role in the pathogenesis of LV systolic chamber dysfunction. As highlighted in chapter 1, the evidence in favour of excess adiposity contributing toward decreases in LV systolic dysfunction is far less substantial than that for diastolic LV function. In the present chapter I will not further elaborate on this evidence as it has been extensively reviewed in chapter 1. Suffice to say however, as demonstrated in chapter 2, whilst strong independent relationships between adiposity indices and LV diastolic function were noted, no independent relationships between adiposity indices and LV systolic function were noted. However, as argued in chapter 1, in the present thesis I proposed that obesity may promote the transition to systolic dysfunction by inducing LVH in excess of that predicted from stroke work. However, I had also indicated in chapter 1 that a number of issues were unresolved in this regard, issues that the present thesis subsequently in-part provided clarity on. Therefore, in the present section I will discuss the results of the present thesis that have contributed toward our knowledge of the role of obesity as a potential determinant of LVH in excess of that predicted by stroke work; the possibility that it is not LVH *per se* that promotes the development of LV systolic chamber dysfunction, but LVH in excess of that predicted by stroke work and the possible mechanisms that may explain obesity-associated LVH in excess of that predicted by stroke work. In the present section I will also suggest further studies required to address either the limitations of the data obtained in the present thesis on the topic of obesity and LVH in excess of that predicted by stroke work or that will further evaluate the hypotheses that have been generated by the present thesis on the topic of obesity and LVH in excess of that predicted by stroke work.

7.3.1 Obesity as a cause of LVH in excess of that predicted by stroke work

In chapter 4 of the present thesis I was able to show that indices of excess adiposity were the principle factors independently associated with LVM in excess of that predicted by stroke work and that these relationships were beyond conventional BP, 24-hour BP, systolic wall stress and aortic PWV. These findings therefore provide strong evidence in favour of

obesity promoting cardiac hypertrophy beyond that which would be expected from increases in haemodynamic loads. These data provide clarity on the unresolved issue of the extent to which excess adiposity promotes cardiac growth beyond workload. In this regard, although a number of studies have demonstrated an increased BMI in those with LVH in excess of that predicted by stroke work (Palmieri et al 1999, Palmieri et al 2001, Calentano et al 2001, Palmieri et al 2004, de Simone et al 2004, Chinali et al 2006, Lopez et al 2007, Chinali et al 2007, Ratto et al 2008), these studies were conducted in select clinical samples and associations were not adjusted for confounders. Moreover, in other select study samples (de Simone et al 2001, Mureddu et al 2001, Muiesan et al 2007, Cioffi et al 2011) obesity was not related to LVM in excess of that predicted by workload even in unadjusted models. Clearly the use of select samples raises the question of a selection bias and a lack of adjustments in studies demonstrating relationships begs the question of whether these relationships are indeed independent of alternative factors. In contrast, in the present thesis I show that BMI and waist circumference were strongly associated with LVM in excess of that predicted by workload in an unselected community-based sample and that these relationships were noted after adjustments for a number of confounders including alternative haemodynamic factors such as systolic wall stress, 24-hour BP and aortic PWV. Thus, if LVM in excess of that predicted by workload is indeed the pathophysiological mechanism responsible for the transition from compensated LVH to LV systolic decompensation, then obesity is most likely to produce LV systolic decompensation only in those in whom LVH exceeds that predicted by workload. In other words, unlike obesity-associated decreases in LV diastolic function, where LVH is not apparently an important pathophysiological process involved, obesity-associated decreases in LV systolic chamber function may depend on the extent of LVH. However, the important question in this regard is whether there is sufficient evidence to suggest that LVM in excess of that predicted by workload is indeed the pathophysiological mechanism responsible for the transition from compensated LVH to LV systolic decompensation? What is the current evidence on this topic and how has the work conducted in the present thesis contributed toward this knowledge?

7.3.2 Is LVM in excess of that predicted by workload the pathophysiological mechanism responsible for the transition from compensated LVH to LV systolic decompensation?

In chapter 4 of the present thesis I describe data to show that independent of a number of confounders including LVM, LVMI, BP and stroke volume; LVM in excess of that predicted by stroke work is inversely associated with absolute ejection fraction in a large, randomly selected community-based sample. Similarly, in chapter 5 of the present thesis I describe data to show that independent of a number of confounders including change in LVM, LVMI, BP and stroke volume, in the treatment of hypertension on-treatment decreases in LVM in excess of that predicted by stroke work are strongly and inversely associated with on-treatment increases in ejection fraction. These data therefore provide not only cross-sectional evidence in a large, unselected community-based sample not subject to false positive or negative findings or a selection bias to verify this hypothesis, but also intervention data to show that LV systolic dysfunction is determined by LVM in excess of that predicted by stroke work rather than LVM or LVMI *per se*. These findings have extended our knowledge of the potential role of LVH in excess of that predicted by workload rather than LVM *per se* as a cause of LV systolic chamber dysfunction. How have these findings contributed toward this field?

Although a number of studies have demonstrated inverse relationships between LVM in excess of that predicted by workload in select clinical samples (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), whether these relationships were independent of absolute or indexed LVM is uncertain. In previous studies reporting on such relations only in the LIFE study did the authors compare the relationships between LV systolic chamber function and either LVM in excess of that predicted by stroke work or LVM (Palmieri et al 2001). In this regard, they noted that LVM was equally as strongly related to EF as LVM in excess of thart predicted by stroke work (Palmieri et al 2001). However, the LIFE study consisted of a select

patient group in that only participants with electrocardiographic evidence of LVH were recruited. Under these circumstances, relationships between absolute LVM and EF may have been more robust and difficult to distinguish from those between LVM in excess of that predicted by stroke work and EF. In contrast however, the data presented in the present thesis from a randomly recruited community-based sample, not subject to a selection bias provides clear evidence that LVM in excess of that predicted by workload is inversely related to EF beyond LVM or LVMI and hence supports the notion that LVH is a compensatory response to workload, but when exceeding that predicted by workload, is associated with LV systolic chamber decompensation.

As indicated in the preceding paragraph, although a number of studies have demonstrated that LVM in excess of that predicted by stroke work is inversely associated with systolic LV chamber 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), and in chapter 4 I have provided evidence to show that these relationships are independent of absolulte LVM and LVMI (Libhaber et al 2012), these relationships have nevertheless been demonstrated in cross-sectional studies and are at odds with on-treatment decreases in systolic LV chamber function associated with LVH regression (Wachtell et al 2002). These relationships may therefore reflect compensatory increases in LVM as a consequence of systolic dysfunction or associated confounding effects. To address these concerns intervention studies designed to regress LVH are required. In this regard, although one prior study has reported that on-treatment regression but not persistence of LVM in excess of that predicted by stroke work is associated with an improved EF (Muiesan et al 2007), whether increases in EF in the participants showing regression of LVM in excess of that predicted by stroke work in that study was independent of or stronger than changes in LVM or LVMI is uncertain. Due to the paucity of data evaluating the impact of regression of LVM in excess of that predicted by stroke work on EF, I evaluated this question as part of the present thesis. In chapter 5, to the best of my knowledge, I provide the first prospective, intervention data to

show that regression of LVH as indexed by LVM in excess of that predicted by stroke work is associated with improvements in EF beyond that of LVM or LVMI.

Therefore, in summary, in the current thesis I have provided substantial evidence to support the notion that LV systolic decompnsation is dependent on LVM in excess of that predicted by workload rather than on LVM or LVMI *per se*. As indicated in the preceding section, obesity is a strong determinant of LVM in excess of that predicted by work load. Thus, the work in the current thesis suggests that obesity could contribute toward LV systolic decompensation, but only when LVH exceeds workload. The question which arises from these data is what are the possible mechanisms responsible for obesity effects on LVM in excess of that predicted by workload or alternative haemodynamic factors?

7.3.3 Insulin resistance as a possible cause of LVH in excess of that predicted by stroke work

As highlighted in chapter 6, a number of studies with small sample sizes conducted in select patient populations (Sharp et al 1992, Sasson et al 1993, Lind et al 1995, Kamide et al 1996, Paolisso et al 1995, Paolisso et al 1997, Tomiyama et al 1997, Vetta et al 1998, Phillips et al 1998, Watanabe et al 1999, Shigematsu et al 2006, Anan et al 2007, Sesti et al 2007) and large study samples (Sundstrom et al 2008, Sciacqua et al 2011, Hwang et al 2011) have provided evidence to support a role for insulin resistance as a possible mechanism involved in increasing LVM. However, in two of the large studies (Sundstrom et al 2008, Hwang et al 2011), the relationships between indices of insulin resistance and LVM were not adjusted for indices of excess adiposity. Furthermore, a number of small studies conducted in select clinical samples (Nagano et al 1994, Kupari et al 1994, Costa et al 1995, Ohya et al 1996, Merudda et al 1998, Jelenc et al 1998, Verdecchia et al 1999, Galvan et al 2000, Malmquist et al 2001, Olsen et al 2003, Ebnic et al 2006) or in large study samples (Chen et al 1998, Sundstrom et al 2000, Devereux et al 2002, Rutter et al 2003, Velagaletti et al 2010, Fox et al 2011, de Simone et al 2003, 2011) have failed to demonstrate a

relationship between indices of insulin resistance and LVM independent of adiposity indices or BP. In this regard, some previous large studies have evaluated relationships between C-peptide (Chen et al 1998) or circulating insulin concentrations (Devereux et al 2002) rather than utilising more accepted approaches to assessing insulin resistance. Moreover, one large study was conducted in elderly men only (Sundstrom et al 2000). Importantly however, in none of these prior studies was the relationship between insulin resistance and LVM in excess of that predicted by workload assessed. In only one study conducted in 53 hypertensives with electrocardiographic LVH from the LIFE study was the irelationship between circulating insulin concentrations or insulin resistance and LVM in excess of that predicted by stroke work assessed (Olsen et al 2004) and in this study no relationships were reported on. The small study sample however raises the question of whether the results reflect a slection bias and a false negative relationship. Thus, in chapter 6 of the present thesis I evaluated whether HOMA-IR, an index of insulin resistance, is associated with LVM in excess of that predicted by stroke work independent of adiposity indices in a relatively large, randomly selected community-based sample with a high prevalence of obesity.

As described in chapter 6, to the best of my knowledge the present study was the first to show that insulin resistance is associated with LVM independent of adiposity indices and beyond that predicted by stroke work (the major haemodynamic factor that determines variations in LVM) and a number of alternative haemodynamic factors including circumferential wall stress, 24- hour BP and aortic PWV. The present study is therefore the first to show that the relationship between insulin resistance and LVM may be accounted for by non-haemodynamic effects. What are the implications of these findings?

7.3.4 Insulin resistance may contribute toward variations in LVM in excess of that predicted by stroke work: Future directions.

Considering that LVM in excess of that predicted by stroke work is a potentially important pathophysiological process involved in the transition to LV systolic dysfunction, the

finding that insulin resistance may contribute toward this structural change requires careful consideration. Without question the results presented in chapters 4-6 raise the question of whether in the absence of diabetes mellitus, obesity, through insulin resistance and the consequent increase in LVM in excess of that predicted by stroke work, may present a risk factor for heart failure by decreasing systolic LV function. The present thesis therefore begs the question of whether targeting insulin resistance may regress LVM in excess of that predicted by stroke work and subsequently improve LV systolic function. Clearly, because the results presented in chapter 4 and 6 were obtained in cross-sectional studies without hard outcomes, as with the conundrum we face with that of the relationships between insulin resistance and LV diastolic function, we need to consider whether we wait for longitudinal studies with hard outcomes to confirm the present results. The results of longitudinal studies with hard outcomes would undoubtedly lend more scientific rigor to the question. Nevertheless, we could also consider beginning small “proof-of-principle” studies to evaluate the possibility that targeting insulin resistance may decreases LVM in excess of that predicted by stroke work and increase systolic LV function. Again, this dilemma obviously requires consideration within the context of a potential epidemic of obesity associated heart failure.

With respect to a potential role for insulin resistance as a cause of LV systolic chamber dysfunction, an additional consideration that emanates from the present thesis is that of the measurement of LV systolic chamber function. As highlighted throughout the thesis, although I employed the well-described method of echocardiography to assess LV systolic chamber function, more recent evidence suggests that left ventricular systolic function as determined using magnetic resonance imaging (global function index) appears to be a more sensitive tool for predicting cardiovascular events (Mewton et al 2013). Further studies using magnetic resonance imaging are therefore required to confirm the results of the present thesis, a task that goes well beyond the resources currently available to researchers in South Africa.

As HOMA-IR was only weakly correlated with LVM_{inappr}, it is important to consider whether targeting individuals with an increased HOMA-IR will necessarily result in the selection of individuals whom are most likely to respond with increases in LV systolic chamber function following the administration of insulin sensitizing agents. Nevertheless, as this relationship translated into a more than 10% difference in LVM_{inappr} between the highest and lowest quartile of HOMA-IR, a size effect that cannot be considered as trivial, one possible approach to ensuring an appropriate result when employing insulin sensitising agents is to select individuals with the highest quartile of HOMA-IR.

7.4 Conclusions

In conclusion, the studies described in the present thesis provide susbtantial evidence in favour of overweight and obesity contributing toward the transition to both diastolic and systolic LV dysfunction independent of confounders including a number of haemodynamic factors, and possibly through the effects of insulin resistance. These findings and how they have advanced our current knowledge in the field have been summarized in Table 7.1. In this regard, the transition to LV diastolic dysfunction although inevitably associated with LVH does not require LVH to produce this change. In contrast, the transition to LV systolic chamber dysfunction is likely to depend on LV growth in excess of that normally produced by stroke work or alternative haemodynamic changes. These studies support the view that targeting insulin resistance may be beneficial in preventing the transition from obesity-associated LVH to LV dysfunction and potentially the development of heart failure. Future longitudinal studies are required to evaluate whether overweight, obesity and the associated insulin resistance predict the development of heart failure associated with either LV systolic or diastolic dysfunction. Moreover, the present studies support the need for “proof-of-principle” studies being conducted with insulin sensitising agents in overweight and obese individuals with insulin resistance and LV diastolic dysfunction or LVH in excess of that predicted by stroke work.

Table 7.1 Summary of the main findings of the present thesis and how they have advanced our current knowledge in the field.

Chapter 2. Provides the first evidence to show that at a community level, waist circumference, an index of excess adiposity, is independently associated with decreases in E/A, an index of mild left ventricular diastolic dysfunction, even beyond left ventricular mass index (LVMI), left ventricular concentric remodelling (as indexed by relative wall thickness [RWT]), aortic stiffness (as indexed by aortic pulse wave velocity) and 24-hour BP. At a community level, waist circumference is second only to age and equivalent to BP in the magnitude of the effect on E/A. This study therefore provides the first evidence to indicate that independent of a number of haemodynamic factors, obesity is an important factor accounting for mild decreases in left ventricular diastolic function.
Chapter 3. Provides the first evidence to show that insulin resistance, as indexed by HOMA-IR is associated with E/A independent of a number of confounders including waist circumference, the main adiposity index that explains variations in E/A. Importantly, these independent relations were also beyond structural LV changes, including LVMI and RWT as well as 24-hour BP and aortic PWV. This study therefore provides the first evidence to indicate that insulin resistance may be an explanation for obesity-associated mild decreases in left ventricular diastolic function.
Chapter 4. Provides the first evidence to show that in a randomly selected community sample, in contrast to a modest or a lack of relationship noted between LVM or LVMI and left ventricular systolic chamber function as indexed by EF, an increased LVM_{inappr} was strongly and independently related to a decreased EF even with adjustments for LVM or LVMI. Moreover, the strength of the relationship between LVM_{inappr} and EF was greater than that of the relations between LVM or LVMI and EF. In a multivariate model with all potential determinants of EF included in the model, LVM_{inappr} was second only to LV systolic wall

stress in contributing toward EF at a community level. Furthermore, indices of excess adiposity were the principle factors independently associated with LVM_{inappr} and these relationships were beyond conventional BP, 24-hour BP, systolic wall stress and aortic PWV. This study therefore provides the first evidence to indicate that independent of a number of haemodynamic factors, obesity, through increases in LVM beyond that predicted by stroke work may be an important cause of decreases in left ventricular systolic chamber function.

Chapter 5. Provides the first evidence to show that in the treatment of mild-to-moderate hypertension over a 4 month period, in contrast to a modest treatment-induced attenuation in EF accompanying decreases in LVM and LVMI, on-treatment decreases in LVM_{inappr} were strongly and independently related to improvements in EF. Importantly, relationships between on-treatment changes in LVM_{inappr} and EF were unaltered by adjustments for LVM or LVMI and were noted to be far stronger than relationships between on-treatment changes in LVM or LVMI and EF. This study therefore provides the first direct evidence to indicate that increases in LVM are an important cause of decreases in left ventricular systolic chamber function, but this depends on the presence of LV hypertrophy beyond that predicted by sroke work.

Chapter 6. Provides the first evidence to show that insulin resistance as indexed by HOMA-IR, is associated with LVM in excess of that predicted by stroke work (LVM_{inappr}) independent of indices of excess adiposity and of a number of haemodynamic factors including circumferential wall stress, 24-hour BP and aortic PWV.

This study therefore provides the first evidence to indicate that independent of a number of haemodynamic factors, inulin resistance may explain obesity-associated increases in LVM beyond that predicted by stroke work and hence decreases in left ventricular systolic chamber function.

References

Allison DB, Faith MS, Heo M, Kotler DP. Hypothesis concerning the U-shaped relation between body mass index and mortality Am J Epidemiol 1997;146:339-349.

Alpert MA, Lambert CR, Panayiotou H, Terry BE, Cohen MV, Massey CV, Hashimi MW, Mukerji V. Relation of duration of morbid obesity to left ventricular mass, systolic function, and diastolic filling, and effect of weight loss. Am J Cardiol 1995 76:1194-1197.

Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am J Med Sci 2001;321:225-236.

Ammar KA, Redfield MM, Mahoney DW, Johnson M, Jacobsen SJ, Rodeheffer RJ. Central obesity: Association with left ventricular dysfunction and mortality in the community. Am Heart J 2008;156:975-981.

Anan F, Yonemochi H, Masaki T, Takahashi N, Fukunaga N, Teshima Y, Iwao T, Kaneda K, Eshima N, Saikawa T, Yoshimatsu H. High0density lipoprotein cholesterol and insulin resistance are independent and additive markers of left ventricular hypertrophy in essential hypertension. Hypertens Res 2007;30:125-31.

Anderson JC, Konz, EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies, Am J Clin Nutr 2001;74:579–584.

Aucott L, Rothnie H, McIntyre L, Thapa M, Waweru C, Gray D. Long-term weight loss from lifestyle intervention benefits blood pressure?: a systematic review. Hypertension 2009;54:756–762.

Aurigemma G, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study, J Am Coll Cardiol 2001;37:1042-1048.

Aurigemma GP, Silver KH, Priest MA, Gaasch WH. Geometric changes allow normal ejection fraction despite a depressed myocardial shortening in hypertensive left ventricular hypertrophy. J Am Coll Cardiol 1995;26:195-202.

Avelar E, Cloward TV, Walker JM, Farney RJ, Strong M, Pendleton RC, Segerson N, Adams TD, Gress RE, Hunt SC, Litwin SE. Left ventricular hypertrophy in severe obesity: interactions among blood pressure, nocturnal hypoxemia, and body mass. Hypertension 2007;49:34-39.

Avignon A, du Cailar G, Ribstein J, Monnier L, Mimran A. Determinants of left ventricular mass in obese patients. Arch Mol Coeur Vaiss 1997;90:1043-046.

Badenhorst D, Veliotes D, Maseko M, Tsotetsi OJ, Brooksbank R, Naidoo A, et al. Beta-adrenergic activation initiates chamber dilatation in concentric hypertrophy. Hypertension 2003;41:449-504.

Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, Szklo M, Lima JA. Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Athersosclerosis) study. J Am Coll Cardiol 2008;51:1775-1783.

Bajraktari G, Koltai MS, Ademaj F, Rexhepaj N, Qirko S, Ndrepepa G, Elezi S. Relationship between insulin resistance and left ventricular diastolic dysfunction in patients with impaired glucose tolerance and type 2 diabetes mellitus. Int J Cardiol 2006;110:206-211.

Barouch LA, Gao D, Chen L, Miller KL, Xu W, Phan AC, Kittleson MM, Minhas KM, Berkowitz DE, Wei C, Hare JM. Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. Circ Res 2006;98:119-124.

Bazzano LA, Belame SN, Patel DA, Chen W, Srinivasan S, McIlwain E, Berenson GS. Obesity and left ventricular dilatation in young adulthood: the Bogalusa Study. Clin Cardiol 2011;34:153-159.

Bella JN, Palmieri V, Roman MJ, Liu JE, Welty TK, Elisa T. Lee ET, Fabsitz RR, Howard BV, Devereux RB. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. Circulation 2002;105:1928-1933.

Bennett CM, Guo M, Dharmage SC. HbA1c as a screening tool for the detection of type 2 diabetes: a systematic review. Diabet Med 2007;24:333-343.

Berkalp B, Cesurb V, Corapcioglub D, Erola C, Baskal N. Obesity and left ventricular diastolic dysfunction. Int J Cardiol 1995;52:23-26.

Bibbins-Domingo K, Pletcher MJ, Lin F, Vittinghof E, Gardin JM, Arynchyn A, Lewis CE, Williams OD, Hulley SB. Racial differences in incident heart failure among young adults. N Engl J Med. 2009;360:1179-1190.

Bing OH, Brooks WW, Robinson KG, Slawsky MT, Hayes JA, Litwin SE, Sen S and Conrad CH. The spontaneously hypertensive rat as a model of the transition from compensated left ventricular hypertrophy to failure. J Mol Cell Cardiol. 1995;27:383-396.

Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson j, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol 2008;52:2148-2155.

Bonara E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care. 2000;15;23:57-63.

Borlaug B, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 2011;123:2006-2014.

Bourne LT, Lambert EV, Steyn K: Where does the black population of South Africa stand on the nutrition transition? Public Health Nutrition 2002;5:157-162.

Brilla CG, Matsubara L and Weber KT. Advanced hypertensive heart disease in spontaneously hypertensive rats. Lisinopril-mediated regression of myocardial fibrosis. Hypertension. 1996;28:269-275.

Brooks WW, Bing OHL, Robinson KG, Slawsky MT, Chaletsky DM and Conrad CH. Effect of angiotensin-converting enzyme inhibition on myocardial fibrosis and function in

hypertrophied and failing myocardium from the spontaneously hypertensive rat. Circulation. 1997;96:4002-4010.

Brooks WW, Shen SS, Conrad CH, Goldstein RH, Bing OHL. Transition from compensated hypertrophy to systolic heart failure in the spontaneously hypertensive rat: structure, function and transcript analysis. Genomics 2012;95:84-92

Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, Cooksey RC. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology 2005;146:5341-5349.

Bugger H, Schwarzer M, Chen D, Schrepper A, Amorim PA, Schoepe M, Nguyen TD, Mohr FW, Khalimonchuk O, Weimer BC, Doenst T. Proteomic remodelling of mitochondrial oxidative pathways in pressure overload-induced heart failure. Cardiovasc Res 2010;85;376-384.

Cadeddu C, Nocco S, Piano D, Deidda M, Cossu E, Baroni MG, Mercuro G. Early impairment of contractility reserve in patients with insulin resistance in comparison with healthy subjects. Cardiovasc Diabetol. 2013, Apr 16.

Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of US adults. N Engl J Med 1999;341:1097-1105.

Caro JF, Dohm LG, Pories WJ, Sinha MK. Cellular alterations in liver and skeletal muscle, and adipose tissue responsible for insulin resistance in obesity and type II diabetes Diabetes Metab Rev 1989;5:665-689.

Carrol JF, Braden DS, Cockrell K, Mizelle HL. Obese hypertensive rabbits develop concentric and eccentric hypertrophy and diastolic filling abnormalities. Am J Hypertens. 1997 Feb;10(2):230-3.

Carroll JF, Zenebe WJ, Strange TB. Cardiovascular function in a rat model of diet-induced obesity. Hypertension 2006;48:65-72.

Casale PN, Devereux RB, Milner M, Zullo G, Harshfield GA, Pickering TG, Laragh JH. Value of echocardiographic measurement of left ventricular mass in predicting

cardiovascular morbid events in hypertensive men. Ann Intern Med. 1986;105:173-178.

Celentano A, Palmieri V, Esposito NDP, Pietropaola I, Crivaro M, Mureddu GF, Devereux RB, de Simone G. Inappropriate left ventricular mass in normotensive and hypertensive patients. Am J Cardiol. 2001;87:361-363.

Chahal NS, Lim TK, Jain P, Chambers JC, Kooner JS, Senior R. New insights into the relationship of left ventricular geometry and left ventricular mass with cardiac function: a population study of hypertensive subjects. Eur Heart J 2010;31:586-594.

Chen CH, Ting TC, Lin SJ, Hsu TL, Ho SJ, Chou P, Chang MS, O'Connor F, Spurgeon H, Lakatta E, Yin FC. Which arterial and cardiac parameter best predict left ventricular mass? Circulation 1998;98:422-428.

Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF, Krumholz HM. Risk factors for heart failure in the elderly: a prospective community based study. Am J Med 1999;106:605-612.

Chinali M, De Marco M, Daddeo G, Benincasa M, Romano C, Galderisi M, de Simone G. Excessive increase in left ventricular mass identifies hypertensive subjects with clustered geometric and functional abnormalities. J Hypertens. 2007;25:1073-1078.

Chinali M, De Simone G, Roman MJ, Lee ET, Best LG, Howard BV, Devereux RB. Impact of obesity on cardiac geometry and function in a population of adolescents. The Strong Heart Study. J Am Coll Cardiol 2006;47:2267-2273.

Cioffi G, Tarantini L, Frizzi R, Stefenelli C, Russo TE, Selmi A, Toller C, Furlanello F, de Simone G. Chronic kidney disease elicits excessive increase in left ventricular mass growth in patients at increased risk for cardiovascular events. J Hypertens. 2011;29:565-573.

Conrad CH, Brooks WW, Hayes JA, Sen S, Robinson KG and Bing OH. Myocardial fibrosis and stiffness with hypertrophy and heart failure in the spontaneously hypertensive rat. Circulation. 1995;91:161-170.

Coort SL, Bonen A, van der Vusse GJ, Glatz JF, Luiken JJ. Cardiac substrate uptake and metabolism in obesity and type-2 diabetes: role of sacolemmal substrate transporters. Mol Cell Biochem. 2007 May;299(1-2):5-18.

Costa CH, Batista MC, Moises VA, Kohlmann NB, Ribeiro AB, Zanella MT. Seum insulin levels, 24-hour blood pressure profile, and left ventricular mass in nonobese hypertensive patients. Hypertension 1995;26:1085-1088.

Cowie MR, Wood DA, Coats AJS, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC. Survival of patients with a new diagnosis of heart failure: a population based study. Heart 2000;83:505-510.

Dahlof B, Devereux RB, Lindholm LH, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Ledeballe-Pdersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H: LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet.2002;359:995-1003.

De Divitiis O, Fazio S, Petitto M, Maddalena G, Contaldo F, Mancini M. Obesity and cardiac function. Circulation 1981;64:477-482.

De Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992;20:1251-1260.

De Simone G, Devereux RB, Chinali M, Roman MJ, Barac A, Panza JA, Lee ET, Howard BV. Sex differences in obesity-related changes in left ventricular morphology: the Strong Heart Study. J Hypertens 2011;29:1431-1438.

De Simone G, Devereux RB, Kimball TR, Mureddu GF, Roman MJ, Contaldo F, Daniels SR. Interaction between body size and cardiac workload: influence on left ventricular mass during body growth and adulthood. Hypertension. 1998;31:1077-1082.

De Simone G, Devereux RB, Palmieri V, Roman MJ, Celentano A, Welty TK, Fabsitz RR, Contaldo F. Howard BV. Relation of insulin resistance to markers of preclinical

cardiovascular disease: the Strong Heart Study. Nutr Metab Cardiovasc Dis 2003;13:140-147.

De Simone G, Kitzman DW, Palmieri V, Liu JE, Oberman A, Hopkins PN, Bella JN, Rao DC, Arnett DK, Devereux RB. Association of inappropriate left ventricular mass with systolic and diastolic dysfunction. Am J Hypertens. 2004;17:828-833.

De Simone G, Kizer JR, Chinali M, Roman MJ, Bella JN, Best LG, Lee ET, Devereux RB. Normalisation for body size and population-attributable risk of left ventricular hypertrophy. The Strong Heart Study. Am J Hypertens 2005;18:191-196.

De Simone G, Palmieri V, Koren MJ, Mensah GA, Roman MJ, Devereux RB. Prognostic implications of the compensatory nature of left ventricular mass in arterial hypertension. J Hypertens 2001;19:119-125.

De Simone G, Verdecchia P, Pede S, Gorini M, Maggioni AP. Prognosis of inappropriate left ventricular mass in hypertension: the MAVI study. Hypertension 2002;40:470-476.

De Simone G[a], Devereux RB, Koren MJ, Mensah GA, Casale PN, Laragh JH. Midwall left ventricular mechanics : An independent predictor of cardiovascular risk in arterial hypertension. Circulation 1996;93:259-265.

De Simone G[a], Devereux RB, Roman MJ, Alderman MH, Laragh JH. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. Hypertension 1994;23:600-606.

De Simone G[b], Devereux RB, Mureddu GF, Roman MJ, Ganau A, Alderman MH, Contaldo F, Laragh JH. Influence of obesity on left ventricular midwall mechanics in arterial hypertension. Hypertension 1996; 28: 276-283.

De Simone G[b], Devereux RB, Roman MJ, Ganau A, Saba PS, Alderman MH, Laragh JH. Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. J Am Coll Cardiol. 1994;23:1444-1451.

De Simone G[c], Devereux RB, Ganau A, Hahn RT, Saba PS, Mureddu F, Roman MJ, Howard BV. Estimation of left ventricular chamber and stroke volume by limited M-

Mode echocardiography and validation by two-dimensional and Doppler echocardiography. Am J Cardiol. 1996;78:801-807.

Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ Campo E, Sachs I, Reichek N. Echocardiograph assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol. 1986;57:450-458.

Devereux RB, de Simone G, Palmieri V, Oberman A, Hopkins P, Kitzman DW, Rao DC, Arnett DK. Relation of insulin to left ventricular geometry and function in African American and white hypertensive adults: the HyperGen study. Am J Hypertens 2002;15:1029-1035.

Dhuper S, Abdullah RA, Weichbrod L, Mahdi E, Cohen HW. Association of obesity and hypertension with left ventricular geometry and function in children adolescents. Obesity 2011;19:128-133.

Dinh W, Lankisch M, Nickl W, Scheyer D, Scheffold T, Kramer F, Klein RM, Coll Barroso M, Füth R. Insulin resistance and glyc emic abnormalities are associated with deterioration of left ventricular diastolic function. A cross-sectional study. Cardiovasc Diabetol 2010;9:63.

Dodd MS, Ball DR, Schroeder MA, Le Page LM, Atherton HJ, Heather LC, Seymour AM, Ashrafian H, Watkins H, Clarke K, Tyler DJ. In vivo alterations in cardiac metabolism and function in the spontaneously hypertensive rat heart. Cardiovasc Res. 2012;95:69-76.

Dong F, Zhang X, Yang X, Esberg LB, Yang H, Zhang Z. Impaired cardiac contractile function in ventricular myocytes from leptin-deficient ob/ob obese mice. Journal of Endocrinology 2006; 188:25-36.

Drazner MH, Rame JE, Marino EK, Gottdiener JS, Kitzman DW, Gardin JM, Manolio TA, Dries DL, Siscovick DS. Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study. J Am Coll Cardiol. 2004;43:2207-2215.

Drazner MH. The progression of hypertensive heart disease. Circulation 2011;123:327-334.

Ebnic H. Ebnic FA, Ozkurt ZN, Dogru T, Yilmaz M. The relationship of LVM to insulin sensitivity and BMI in healthy individuals. Acta Cardiology. 2006;61:398-405.

Eckel RH, Barouch WW, Ershow AG. Report of the National Heart, Lung, and Blood Institute—National Institute of Diabetes and Digestive and Kidney Diseases Working Group on the pathophysiology of obesity-associated cardiovascular disease, Circulation 2002;10:2923–2928.

Elmer PJ, Obarzanek E, Vollmer WM, Simons-Morton D, Stevens VJ, Young DR, Lin PH, Champagne C, Harsha DW, Svetkey LP, Ard J, Brantley PJ, Proschan MA, Erlinger TP, Appel LJ. Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. Ann Intern Med 2006;144:485–495.

Esler M, Rumantis N, Wiesner G, Kaye D, Hastings J, Lambert G. Sympathetic nervous system and insulin resistance. From obesity to diabetes. Am J Hypertens 2001;14:304S-309S.

Esposito G, Rapacciulo A, Naga Prasad SV, Takaoka H, Thomas SA, Koch WJ and Rockman HA.Genetic alterations that inhibit in vivo pressure overload hypertrophy prevent cardiac dysfunction despite increased wall stress. Circulation. 2002;05:85-92.

Fischer M, Baessler A, Hense HW, Hengstenberg C, Muscholl M, Holmer S, Doring A, Broeckel U, Riegger G, Schunkert H. Prevalence of left ventricular diastolic dysfunction in the community: Results from a Doppler echocardiographic-based survey of a population sample. Eur Heart J 2003;24:320-328.

Fox E, Taylor H, Andrew M, Han H, Mohamed E, Garrison R, Skelton T. Body mass index and blood pressure influences on left ventricular mass and geometry in African Americans. The Atherosclerosis Risk and Communities (ARIC) Study. Hypertension 2004;44:55-60.

Fox ER, Sarpong DF, Cook JC, Samdashi TE, Nagarajarao HS, Liebson PR, Sims M, Howard G, Garrison R, Taylor HA Jr. The relation of diabetes, impaired fasting blood

glucose and insulin resistance to left ventricular structure and function in African Americans: the Jackson Heart Study. Diabetes Care. 2011;34:507-9

Frohlich ED, Gonzalez A, Diez J. Hypertensive left ventricular hypertrophy risk: beyond adaptive cardiomyocyte hypertrophy. J Hypertens 2010:29:17-26.

Galderisi M, Paolisso G, Tagliamonte MR, Alfieri A, Petrocelli A, de Divitiis M, Varricchio M, de Divitiis O. Is insulin action a determinant of left ventricular relaxation in uncomplicated essential hypertension? J Hypertens. 1997 Jul;15(7):745-50.

Galvan AQ, Galetta F, Natali A,Muscelli, Sironi AM, Cini G, Camastra S, Ferrannini E. Insulin resistance and hyperinsulinaemia: No independent relation to left ventricular mass in humans. Circulation.2000;102;2233-2238.

Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Varqiu P, Laragh JH. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am Coll Cardiol 1992 Jun;19(7):1550-8.

Gardin JM, McClelland R, Kitzman D, Lima JAC, Bommer W, Klopfenstein HS, Wong ND, Smith VE, Gottdiener J. M-mode echocardiographic predictors of six-to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (The Cardiovascular Health Study). Am J Cardiol.2001;87:1051-1057.

Gardin JM, Wagenknecht LE, Anton-Culver H, Flack F, Gidding S, Kurosaki T, Wong ND, Manolio TA. Relationship of cardiovascular risk factors to echocardiographic left ventricular mass in healthy young black and white adult men and women: The CARDIA Study (Coronary Artery Risk Development in Young Adults). Circulation 1995;92:380-387.

Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. Ann Intern Med 1992;117:831-836.

Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol. 2000;35:1628-1637.

Gottdiener JS, Reda DJ, Materson BJ, Massie BM, Notargiacomo A, Hamburger RJ, Williams DW, Henderson WG. Importance of obesity, race and age to the cardiac structural and functional effects of hypertension. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. J Am Coll Cardiol 1994;24:1492-1498.

Gu D, He J, Duan X, Reynolds K, Wu X, Chen J, Huang G, Chen CS, Whelton PK. Body weight and mortality among men and women in China. JAMA 2006;295:776-783.

Gutin B, Treiber F, Owens S, Mensah GA. Relations of body composition to left ventricular geometry and function in children. J Paediatr 1998;132:1023-1027.

Hartford M, Wikstrand JC, Wallentin I, Ljungman SM, Berglund GL. Left ventricular wall stress and systolic function in untreated primary hypertension. Hypertension 1985;7:97-104.

He J, Ogden LG, Bazzano LA, Vuppturi S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women:NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161:996-1002.

Hedayati SS, Elsayed EF, Reilly RF. Non-pharmacological aspects of blood pressure management: what are the data? Kidney Int 2011;79:1061–1070.

Heitmann BL, Erikson H, Ellsinger BM, Mikkelsen KL, Larsson B. Mortality associated with body fat, fat-free mass and body mass index among 60-year-old Swedish men: a 22-year follow-up. The study of men born in 1913. Int J Obes Relat Metab Disord. 2000;24,33-37.

Hernandez AM, Huber JS, Murphy ST, Janabi M, Gengsheng LZ, Brennan KM, O'Neil JP, Seo Y, Gullberg GT. Longitudinal evaluation of left ventricular substrate metabolism, perfusion and dysfunction in the spontaneously hypertensive rat model of hypertrophy using microPET/CT imaging. Journal of Nuclear Medicine 2013;(Epub)

Holland DJ, Kumbhani DJ, Ahmed SH, Marwick TH. Effects of treatment on exercise tolerance, cardiac function, and mortality in heart failure with preserved ejection fraction. A meta-analysis. J Am Coll Cardiol 2011;57:1676-1686.

Hsuan C-F, Huang C-K, Lin J-W, Lin L-C, Lee T-L, Tai C-M, Yin W-H, Tseng W-K, Hsu K-L, Wu C-C. The effect of surgican weight reduction on left ventricular structure and function in severe obesity. Obesity 2010;18:1188-1193.

Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Jacobs AK, Hiratzka LF, Russell RO, Smith SC, Jr. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary, a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration with the International Society for Heart and Lung Transplantations; endorsed by the Heart Failure Society of America. Circulation 2001;104:2996-3007.

Hwang YC, Jee JH, Kang M, Rhee EJ, Sung J, Lee MK. Metabolic syndrome and insulin resistance are associated with abnormal left ventricular diastolic function and structure independent of blood pressure and fasting plasma glucose level. Int J Cardiol. 2012; 23:107-11.

Iacobellis G, Ribaudo MC, Leto G, Zappaterreno A, Vecci E, DiMario U, Leonetti F. Influence of excess fat on cardiac morphology and function. Study in uncomplicated obesity. Obes Res 2002;10:767-773.

Ilercil A, Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Welty TK, Robbins DC, Fabsitz RR, Howard BV, Lee ET. Relationship of impaired glucose tolerance to left ventricular structure and function: the Strong Heart Study. Am Heart J. 2001;141:992-998.

Ingelsson E[a], Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. J Am Med Ass 2005;294:334-341.

Ingelsson E[b], Arnlov J, Sundstrom J, Lind L. Inflammation, as measured by the erythrocyte sedimentation rate, is an independent predictor for the development of heart failure. J Am Coll Cardiol 2005 ;45:1802-1806.

Jee SH, Sull JW, Park J, Lee SY, Ohrr H, Guallar E, Samet JM. Body mass index and mortality in Korean men and women. N Engl J Med 2006;355:779-787.

Jelenc M, Zemva A, Marn-Pernat A, Zemva Z. Are insulin metabolsim and night-time blood pressure related to left ventricular hypertrophy? Int J Cardiol 1998;28:261-265.

Johansson S, Wallander MA, Ruigomez A, Garcia Rodriguez LA. Incidence of newly diagnosed heart failure in UK general practice. Eur J Heart Fail 2001;3:225-231.

Jordan J, Yumuk V, Schlaich M, Nilsson PM, Zahorska-Markiewicz B, Grassi G, Schmieder RE, Engeli S, Finer N. Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: obesity and difficult to treat arterial hypertension. J Hypertens 2012;30:1047-1055.

Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest. 2000;106:473–481.

Kamide K, Nagano M, Nakano N, Yo Y, Kobayashi R, Rakugi H, Higaki J, Ogihara T. Insulin resistance and cardiovascular complications in patients with essential hypertension. Am J Hypertens. 1996 Dec;9(12 Pt 1):1165-71.

Kannel, WB, Gordon T, Castelli WP and Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham study. Ann Intern Med 1970;72:813-822.

Karason K, Wallentin I, Larsson B, Sjöström L. Effects of obesity and weight loss on cardiac function and valvular performance. Obes Res 1998;6:422-429.

Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson SD, Kannel WB, Vasan RS. Obesity and the risk of heart failure. New Engl J Med 2002;347:305-313.

Kenchaiah S, Sesso HD, Gaziano MJ. Body mass index and vigorous physical activity and the risk of heart failure among men. Circulation 2009;119:44-52.

Kizer JR, Arnett DK, Bella JN, Paranicas M, Rao DC, Province MA, Oberman A, Kitzman DW, Hopkins PN, Liu JE, Devereux RB. Differences in left ventricular structure between black and white hypertensive adults. The Hypertension Genetic Epidemiology Network Study. Hypertension 2004;43:1182-1188.

Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, Hong Y, Eckel RH. American Heart Association Council on Nutrition, Physical Activity, and Metabolism and American College of Cardiology Foundation, Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation, Circulation 2004;110:2952–296.

Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345-352.

Kupari M, Koshinen P, Virolainen J. Correlates of left ventricular mass in a population sample aged 36-37 years. Circulation 1994;89:1041-1050.

Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE. Body mass index and the risk of stroke in men. Arch Intern Med. 2002;162:2557-2562.

Lahmann PH, Lissner L, Gullberg B, Berglund G. A prospective study of adiposity and all-cause mortality: the Malmo Diet and Cancer Study Obes Res. 2002;10,361-369.

Lambert E, Sari CI, Dawood T, Nguyen J, McGrane M, Eikelis N, Chopra R, Wong C, Chatzivlastou K, Head G, Straznicky N, Esler, Schlaich M, Lambert G. Sympathetic nervous system activity is associated with obesity-induced subclinical organ damage in young adults. Hypertension 2010;56:351-358.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MJ, Stewart WJ. Recommendations for chamber quantification: A report from the American

Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-1463.

Latner J, Wilson G, Stunkard A, Jackson M. Self-help and long-term behavior therapy for obesity, Behav Res Ther. 2002;40:805–812.

Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry. The Framingham Heart Study. JAMA 1991;266:231-236.

Lauer MS, Anderson KM, Levy D. Separate and joint influences of obesity and mild hypertension on left ventricular mass and geometry: The Framingham Heart Study. J Am Coll Cardiol 1992;19:130-134.

Leichman JG[a], Aguilar D, King TM, Mehta S, Majka C, Scarborough T, Wilson EB, Taegtmeyer H. Improvements in systemic metabolism, anthropometrics and left ventricular geometry three months after bariatric surgery. Surg Obes Relat Dis 2006;2:592-599.

Leichman JG[b], Aguilar D, King TM, Vlada A, Reyes M, Taegtmeyer H. Association of plasma free fatty acids and left ventricular diastolic function in patients with clinically severe obesity. Am J Clin Nutr 2006;84:336-341.

Leichman JG, Wislon EB, Scarborough T, Aguilar D, Miller CC, Yu S, Algahim MF, Reyes M, Moody FG, Taegtmeyer H. Dramatic reversal of derangements in muscle metabolism and diastolic left ventricular function after bariatric surgery. Am J Med 2008;121:966-973.

Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographic measurement of left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561-1566.

Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557-1562.

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

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

Libhaber E, Woodiwiss AJ, Libhaber C, Maseko M, Majane OHI, Makaula S, Dessein P, Essop MR, Sareli P, Norton GR. Gender-specific brachial artery blood pressure-independent relationship between pulse wave velocity and left ventricular mass index in a group of African ancestry. J Hypertens 2008;26:1619-1628.

Lind L, Andersson et al PE, Andren B, Hanni A, Lithell HO. Left ventricular hypertrophy in hypertension is associated with the insulin resistance metabolic syndrome. J Hypertens 1995;13:433-438.

Liu JJ, Peng L, Bradley CJ, Zulli A, Shen J and Buxton BF. Increased apoptosis in the heart of genetic hypertension, associated with increased fibroblasts. Cardiovasc Res. 2000;45:729-735.

Lonn E, Shaikholeslami R, Yi Q, Bosch J, Sullivan B, Tanser P, Magi A, Yusuf S. Effect of ramipril on left ventricular mass and function in cardiovascular patients with controlled blood pressure and presrved left ventricular ejection fraction. : a substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial. J Am Coll Cardiol. 2004;43:2200-2206.

Lopez B, Castellano JM, Gonzalez A, Braba J, Diez J. Association of increased plasma cardiotrophin-1 with inappropriate left ventricular mass in essential hypertension. Hypertension 2007;50:977-983.

Lorber R, Gidding SS, Daviglus ML, Colangelo LA, Liu K, Gardin JM. Influence of systolic blood pressure and body mass index on left ventricular structure in healthy African-American and white young adults: the CARDIA study. J Am Coll Cardiol 2003; 41(6):955-960.

Mackey RH, Sutton-Tyrrell K, Vaitkevicius PV, Sakkinen PA, Lyles MF, Spurgeon HA, Lakatta EG, Kuller LH. Correlates of aortic stiffness in elderly individuals: a subgroup of the Cardiovascular Health Study. Am J Hypertens 2002;15:16-23.

Maunganidze F, Norton GR, Maseko MJ, Libhaber CD, Majane OH, Sareli P, Woodiwiss AJ. Relationship between glomerular dysfunction and left-ventricular mass independent of haemodynamic factors in a community sample. *J Hypertens*. 2013 Mar;31(3):568-75.

Majane OHI, Norton GR, Maseko MJ, Makaula S, Crowther N, Paiker J, Thijs L, Brooksbank R, Sareli P, Staessen JA, Woodiwiss AJ. The association of waist circumference with ambulatory blood pressure is independent of alternative adiposity indices. J Hypertens 2007;25:1798-1806.

Majane OHI, Vengethasamy L, du Toit EF, Makaula S, Woodiwiss AJ, Norton GR. Dietary-induced obesity hastens the progression from concentric cardiac hypertrophy to pump dysfunction in spontaneously hypertensive rats. Hypertension 2009;54:1376-1383.

Majane OHI, Woodiwiss AJ, Maseko MJ, Crowther N, Dessein P, Norton GR. Impact of age on the independent association of adiposity with pulse wave velocity in a population sample of African ancestry. Am J Hypertens 2008;21:936-942.

Malmqvist K, Kahan T, Edner M, Held C, Hagg A, Lind L, Muller Brunotte R, Nystrom F, Ohman KP, Osbakken MD, Ostergern J. Regression of left ventricular hypertrophy in human hypertension with irbesartan. J Hypertens. 2001; 19:1167-1176.

McGee DL. Body mass index and mortality: A meta-analysis based on person-level data from twenty-six observational studies. Ann Epidemiol 2005;15:87-97.

Mensah GA, Treiber FA, Kapuku GK, Davis H, Barnes VA, Strong WB. Patterns of body fat deposition in youth and their relation to left ventricular markers of adverse cardiovascular prognosis. Am J Cardiol 1999;84:583-588.

Messerli FH, Sundgaard-Riise K, Reisin ED, Dreslinski GR, Ventura HO, Oigman W, Frohlich ED, Dunn FG. Dimorphic cardiac adaptation to obesity and arterial hypertension. Ann Intern Med 1983;99:757-761.

Messerli FH. Cardiovascular effects of obesity and hypertension. Lancet 1982 May 22l;1;1168-8.

Mewton N, Opdahl A, Choi EY, Almeida AL, Kawel N, Wu CO, Burke GL, Liu S, Bluemke DA, Lima JA. Left ventricular global index by magnetic resonance imaging—a novel marker for assessment of cardiac performance for the prediction of cardiovascular events: the multi-ethnic study of atherosclerosis. Hypertension 2013 Apr 61(4):770-8.

Milani RV, Lavie CJ, Mehra MR, Ventura HO, Kurtz JD, Messerli FH. Left ventricular geometry and survival in patients with normal left ventricular ejection fraction. Am J Cardiol 2006;97:959-963

Mokdad A, Ford E, Bowman B, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003;289:76-79.

Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001;286:1195-1200.

Muiesan ML, Salvetti M, Paini A, Monteduro C, Galbassini G, Bonzi B, Poissa P, Belotti E, Rosei A, Rizzoni D, Castellano M, Rosei EA. Inappropriate left ventricular mass changes during treatment adversely affects cardiovascular prognosis in hypertensive patients. Hypertension 2007;49:1077-1083.

Mureddu GF, Cioffi G, Stefenelli C, Boccanelli A, de Simone G. Compensatory or inappropriate left ventricular mass in different models of left ventricular pressure overload: comparison between patients with aortic stenosis and arterial hypertension. J Hypertens 2009;27:642-649.

Mureddu GF, de Simone G, Greco R, Rosato GF, Contaldo F. Left ventricular filling pattern in uncomplicated obesity. Am J Cardiol 1996;77:509-514.

Mureddu GF, Greco R, Rosato GF, Cella A, Vaccaro O, Contaldo F, de Simone G. Relation of insulin resistance to left ventricular hypertrophy and diastolic dysfunction in obesity. Int J Obes Relat Metab Disord 1998;22:363-368.

Mureddu GF, Pasanisi F, Palmieri V, Celentano A, Contaldo F, de Simone G. Appropriate or inappropriate left ventricular mass in the presence or absence of prognostically adverse left ventricular hypertrophy. J Hypertens 2001;19:1113-1119.

Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJ. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15 000 middle-aged men and women (the Renfrew-Paisley study. Eur Heart J 2006;27:96-106.

Must A, Spadano J, Oakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282:1523-1529.

Nagano N, Nagano M, Yo Y, Liyama K, Higaki J, Mikami H, Ogihara T. Role of glucose intolerance in cardiac diastolic function in essential hypertension. Hypertension 1994;23:1002-1005.

Nicklas BJ, Cesari M, Penninx BWJH, Kritchevsky SB, Ding J, Newman A, Kitzman DW, Kanaya AM, Pahor M, Harris TB. Abdominal obesity is an independent risk factor for chronic heart failure in older people. J AM Geriatr Soc 2006;54:413-420.

Niemann B, Chen Y, Teschner M, Li L, Silber RE, Rohrbach S. Obesity induces signs of premature cardiac aging in younger patients: the role of mitochondria. J Am Coll Cardiol 2011;57:577-585.

Nikolaidis LA, Sturzu A, Stolarski C, Elahi D, Shen YT, Shannon RP. The development of myocardial insulin resistance in conscious dogs with advanced dilated cardiomyopathy. Cardiovasc Res 2004;61:297-306.

Norton GR, Majane OHI, Libhaber E, Maseko MJ, Makaula S, Libhaber C, Woodiwiss AJ. The relationship between blood pressure and left ventricular mass index depends on an excess adiposity. J Hypertens 2009;27:1873-1883.

Norton GR, Maseko M, Libhaber E, Libhaber CD, Majane OHI, Dessein P, Sareli P, Woodiwiss AJ. Is pre-hypertension an independent predictor of target organ changes in young-to-middle aged persons of African descent? J Hypertens 2008;26:2279-2287.

Norton GR, Tsotetsi J, Trifunovic B, Hartford C, Candy GP and Woodiwiss AJ. Myocardial stiffness is attributed to alterations in cross-linked collagen rather than total collagen or phenotypes in spontaneously hypertensive rats. Circulation. 1997;96:1991-1998.

Norton GR, Woodiwiss AJ, Gaasch WH, Mela T, Chung ES, Aurigemma GP and Meyer TE. Heart failure in pressure overload hypertrophy: the relative roles of ventricular remodeling and myocardial dysfunction. J Am Coll Cardiol. 2002;39:664-671.

Nunez E, Arnett DK, Benjamin EJ, Liebson PR, Skelton TN, Taylor H, Andrew MS. Optimal threshold value for left ventricular hypertrophy in blacks from the Atherosclerosis Risk in Communities study. Hypertension 2005;45:58-63.

O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens. 2003; 21:821-848.

Ogden CL, Yanovski SZ, Carroll MD, Flegal KM. The epidemiology of obesity. Gastroenterology 2007;132:2087-102.

Ohya Y, Abe I, Fujii K, Ohmori S, Onaka U, Kobayashi K, Fujishima M. Hyperinsulinemia and left ventricular geometry in a work-site population in Japan. Hypertension 1996;27:729-734.

Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snappinn S, Harris KE, Aurup P, Edelman JM and Dahlof B. Regression of electrocardiographic left

ventricular hypertrophy by losartan versus atenolol: The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. Circulation.2003;108:684-690.

Olsen MH, Hjerkinn E, Wachtell K, Hoieggen A, Bella JN, Nesbitt SD, Fossum E, Kjeldsen SE, Julius S, Ibsen H. Are left ventricular mass, geometry and function related to vascular changes and/or insulin resistance in long-standing hypertension? ICARUS: a LIFE substudy. J Hum Hypertens 2003;17:305-311.

Olsen MH, Wachtell K, de Simone G, Palmieri V, Dige-Peterson H, Devereux RB, Ibsen H, Rokkedal J. Is inappropriate left ventricular mass related to neurohormonal factors and/or arterial changes in hypertension? A LIFE substudy. J Hum Hypertens 2004;18:437-443.

Ouwens DM, Boer C, Fodor M, De Galan P, Heine RJ, Maassen JA, Diamant M. Cardiac dysfunction induced by high fat diet is associated with altered myocardial insulin signalling in rats. Diabetologia, 2005;48:1229-1237.

Owan T, Avelar E, Morley K, Jiji R, Hall N, Krezowski J, Gallagher J, Williams Z, Preece K, Gundersen N, Strong MB, Pendleton RC, Segerson N, Cloward TV, Walker JM, Farney RJ, Gress RE, Adams TD, Hunt SC, Litwin SE. Favorable changes in cardiac geometry and function following gastric bypass surgery: 2-year follow-up in the Utah obesity study. J Am Coll Cardiol.2011 Feb 8;57(6):732-9

Palmieri V, de Simone G, Arnett DK, Bella JN, Kitzman DW, Oberman A, Hopkins PN, Province MA, Devereux RB. Relation of various degrees of body mass index in patients with systemic hypertension to left ventricular mass, cardiac output, and peripheral resistance (The Hypertension Genetic Epidemiology Network Study). Am J Cardiol 2001 Nov 15;88(10):1163-8.

Palmieri V, de Simone G, Roman MJ, Schwartz JE, Pickering TG, Devereux RB. Ambulatory blood pressure and metabolic abnormalities in hypertensive subjects with inappropriately high left ventricular mass. Hypertension 1999;34:1032-1040.

Palmieri V, Wachtell K, Bella JN, Gerdts E, Papademetriou V, Nieminen MS, Dahlöf B, Roman MJ, Devereux RB. Usefulness of the assessment of the appropriateness of

left ventricular mass to detect left ventricular systolic and diastolic abnormalities in absence of echocardiographic left ventricular hypertrophy: the LIFE study. J Hum Hypertens 2004;18:423-430.

Palmieri V, Wachtell K, Gerdts E, Bella JN, Papademetriou V, Tuxen C, Nieminen M, Dahlof B, de Simone G, Devereux RB. Left ventricular function and hemodynamic features of inappropriate left ventricular hypertrophy in patients with systemic hypertension: the LIFE Study. Am Heart J. 2001;141:784-791.

Paolisso G, Galderisi M, Tagliamonte MR, De Divitis M, Galzerano D, Petrocelli A, Gualdiero P, De Divitis O, Varricchio M. Myocardial wall thickness and left ventricular geometry in hypertensives. Relation with insulin. Am J Hypertens 1997;10:1250-1256.

Paolisso G, Galzerano D, Gambardella A, Gentile S, Lama D, Varricchio M. Low fasting and insulin-mediated intracellular magnesium accumulation in hypertensive patients with left ventricular hypertrophy and dysfunction: role of insulin resistance. J Hum Hypertens 1995;9:1153-116.

Pascual M, Pascual DA, Soria F, Vicente T, Hernández AM, Tébar FJ, Valdés M. Effects of isolated obesity on systolic and diastolic left ventricular function. Heart 2003;89;1152-1156.

Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539-2550.

Perlini S, Muiesan ML, Cuspidi C, Sampieri L, Trimarco B, Aurigemma GP, Agabiti-Rosei E, Mancia G. Midwall mechanics are improved after regression of hypertensive left ventricular hypertrophy and normalization of chamber geometry. Circulation. 2001;103:678-683.

Perri M, Corsica J. Improving the maintenance of weight lost in behavioral treatment of obesity. In: T.A. Wadden and A. Stunkard, Editors, Handbook of obesity, The Guilford Press, New York (2002), pp. 357–394.

Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Barzilai B, Davila-Roman VG. Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. J Am Coll Cardiol 2004;43:1399-1404.

Peterson LR, Waggoner AD, Schechtmann KB, Meyer T, Gropler RJ, Barzilia B, Davila-Romain VG. Alterations in left ventricular structure and function in young healthy obese women. J Am Coll Cardiol 2004;43:1399–1404.

Peterson LR, Waggoner AD, Schechtmann KB, Meyer T, Gropler RJ, Barzilia B, Davila-Romain VG. Alterations in left ventricular structure and function in young healthy obese women. J Am Coll Cardiol 2004;43:1399–1404.

Phillips RA, Krakoff LR, Dunaif A, Finegood DT, Gorlin R, Shimabukuro S. Relation among left ventricular mass, insulin resistance and blood pressure in nonobese subjects. J Clin Endocrinol Metab.1998:83:4284-4288.

Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, Jones DW, Kurtz T, Sheps SG, Rocella EJ. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: Blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005;45:142-161.

Pischon T, Boeing H, Hoffman K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008;359:2105-2120.

Poirier P, Giles TD, Bray GA, Hung Y, Stern JS, Pi-Sunyer FX, Eckel RH. Obesity and cardiovascular disease: pathophysiology, evaluation and effect of weigh loss: An update on the American Heart Association Scientific Statement on Obesity and Heart

Disease from the Obesity Committee of the Council on Nutrition, Physical Activity and Metabolsim. Circulation 2006;113:898-918.

Powell BD, Redfield MM, Bybee KA, Freeman WK, Rihal CS. Association of obesity with left ventricular remodeling and diastolic dysfunction in patients without coronary artery disease. Am J Cardiol 2006;98:116-120.

Puoane T, Steyn K, Bradshaw D, Laubscher R, Fourie J, Lambert V, Mbananga N. Obesity in South Africa: the South African demographic and health survey. Obes Res 2002;10:1038-1048.

Ratto E, Leoncini G, Viazzi F, Bezante GP, Falqui V, Parodi A, Conti N, Tomolillo C, Deferrari G, Pontrmoli R. Inappropriate left ventricular mass is associated with microalbuminuria independently of left ventricular hypertrophy in primary hypertension. J Hypertens 2008;26:345-350.

Reaven GM. Importance of identifying the overweight patient who will benefit the most by losing weight. Ann Intern Med. 2003;138:420-3.

Redelinghuys M, Norton GR, Scott L, Maseko MJ, Brooksbank R, Majane OH, Sareli P, Woodiwiss AJ. Relationship between urinary salt excretion and pulse pressure and central aortic hemodynamics independent of steady state pressure in the general population. Hypertension 2010;56:584-590.

Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: Appreciating the scope of the heart failure epidemic. JAMA 2003;289:194-202.

Relling DP, Esberg LB, Fang CX, Johnson WT, Murphy EJ, Carlson EC, Saari JT, Ren J. High-fat diet-induced juvenile obesity leads to cardiomyocyte dysfunction and upregulation of Foxo3a transcription factor independent of lipotoxicity and apoptosis. Journal of Hypertension 2006; 24:549-561.

Ren J, Sowers JR, Walsh MF, Brown RA. Reduced contractile response to insulin and IGF-I in ventricular myocytes from genetically obese Zucker rats. Am J Physiol Heart Circ Physiol 2000; 279: H1708-H1714.

Reutter BW, Huesman RH, Brennan KM, Boutchko R, Hanrahan SM, Gullberg GT. Longitudinal evaluation of fatty acid metabolism in normal and spontaneously hypertensive rat hearts with dynamic microSPECT imaging. Int J Mol Imaging 2011;2011:893129.

Rider OJ, Francis JM, Ali MK, Petersen SE, Robinson M, Robson MD, Byrne JP, Clarke K, Neubauer S. Beneficial cardiovascular effects of bariatric surgical and dietary weight loss in obesity. J Am Coll Cardiol. 2009 Aug 18;54(8):718-26.

Rider OJ, Peterson SE, Francis JM, Ali MK, Hudsmith LE, Robinson MR, Clarke K, Neubauer S. Ventricular hypertrophy and cavity dilatation in relation to body mass index in women with uncomplicated obesity. Heart 2011;97:203-208.

Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Tullio MR. Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. J Am Coll Cardiol 2011;57:1368-1374.

Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, Nesto RW, Wilson PWF, Vasan RS. Impact of glucose intolerance and insulin resistance on cardiac structure and function. Sex related differences in the Framingham Heart Study. Circulation. 2003;107:448-454.

Sahn DJ, De Maria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurement. Circulation. 1978; 58: 1072-1083.

Samuelsson AM, Bollano E, Mobini R, Larsson BM, Omerovic E, Fu M, Waagstein F, Holmäng A. Hyperinsulinemia: effect on cardiac mass/function, angiotensin II receptor expression, and insulin signaling pathways. Am j Physiol Heart Circ Physiol. 2006 Aug;291(2):H787-96.

Santos JLF, Salemi VMC, Picard MH, Mady C, Coelho OR. Subclinical regional left ventricular dysfunction in obese patients with and without hypertension or hypertrophy. Obesity 2011;19:1296-1303.

Sareli P, Radevski IV, Valtchanova ZP, Libhaber E, Candy GP, Hond ED, Libhaber C, Skudicky D, Wang JG, Staessen J. Efficacy of different drug classess used to initiate antihypertensive treatment in black subjects. Arch Intern Med. 2001;161:965-971.

Sasson Z, Rasooly Y, Bhesania T, Rasooly I. Insulin resistance is an important determinant of left ventricular mass in the obese. Circulation.1993;88:1431-1436.

Scaglione R, Dichiara MA, Indovina A, Lipari R, Ganguzza A, Parrinello G, Capuana G, Merlino G, Licata G. Left ventricular diastolic and systolic function in normotensive obese subjects: influence of degree and duration of obesity. Eur Heart J 1992;13(6):738-742.

Schillaci G, Pasqualini L, Verdecchia P, Vaudo G, Marchesi S, Percellati C, de Simone G, Mannarino E. Prognostic significance of left ventricular diastolic dysfunction in essential hypertension. J Am Coll Cardiol 2002;39:2005-2011.

Schlaich MP, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. Circulation. 2003;108:560-565.

Sciacqua A, Miceli S, Carullo G, Greco L, Succurro E, Arturi F, Sesti G, Perticone F. One-hour postload plasma glucose levels and left ventricular mass in hypertensive patients. Diabetes Care. 2011 Jun;34(6):1406-11.

Sesti G, Sciacqua A, Scozzafava A, Vatrano M, Angotti E, Ruberto C, Santillo E, Parlato G, Perticone F. Effects of growth hormone and insulin-like growth factor-1 on cardiac hypertrophy of hypertensive patients. J Hypertens 2007;25:471-477.

Sharp SD, Wllliams RR. Fasting insulin and left ventricular mass in hypertensives and normotensive controls. Cardiology 1992;81:207-212.

Sherif K, Barrett M, Kushner H, Falkner B. The association of left ventricular mass with cardiovascular risk factors in African American women. American Journal of the Medical Sciences 2000; 320(1):13-17.

Shiburi CP, Staessen JA, Maseko M, Wojciechowska W, Thijs L, van Bortel LM, Woodiwiss AJ, Norton GR. Reference values for Sphygmocor measurements in South Africans of African ancestry. Am J Hypertens 2006;19:40-46.

Shigematsu Y, Norimatsu S, Ohtsuka T, Okayama H, Higaki J. Sex-related differences in the relations of insulin resistance and obesity to left ventricular hypertrophy in Japanese hypertensive patients. Hypertens Res 2006;29:499-504.

Shimizu G, Hirota Y, Kita Y, Kawamura K, Saito T, Gaasch WH. Left ventricular midwall mechanics in systemic arterial hypertension: myocardial function is depressed in pressure-overload hypertrophy. Circulation 1991;83:1676-1684.

Skilton MR, Sieveking DP, Harmer JA, Franklin J, Loughnan G, Nakhla S, Sullivan DR, Caterson ID, Celermajer DS. The effects of obesity and non-pharmacological weight loss on vascular and ventricular function and structure. Diabetes, Obesity Metab 2007;10:1-11.

Skudicky D, Sareli P, LIbhaber E, Candy G, Radevski I, Valtcanova Z, Tshele E, Thijs L, Wang J-G, Staessen JA. Relationship between treatment-induced changes in left ventricular mass and blood pressure in black African hypertensive patients. Circulation. 2002;105:830-836.

Sliem H, Nasr G. Left ventricular structure and function in prediabetic adults: Relationship with insulin resistance. J Cardiovasc Dis Res 2011;2:23-28.

Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, Becker A, Stewart S. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. Lancet 2008;371:915-922.

Spies C, Farzaneh-Far R, Na B, Kanaya A, Schiller N, Whooley MA. Relations of obesity to heart failure hospitalization and cardiovascular events in persons with stable coronary heart disease (from the Heart and Soul Study). Am J Cardiol 2009;104:883-889.

Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315-322.

Stewart S, Wilkinson D, Hansen C, Vaghela V, Mvungi R, McMurray J, Sliwa K. Predominance of heart failure in the heart of Soweto study cohort: Emerging challenges for urban African communities. Circulation 2008;118:2360-2367.

Steyn K, Sliwa K, Hawken S, Commerford P, Onen C, Damasceno A, Ounpuu S, Yusuf S; INTERHEART Investigators in Africa. Risk factors associated with myocardial infarction in Africa: the INTERHEART Africa study. Circulation. 2005;112:3554-61.

Stoddard MF, Tseuda K, Thomas M, Dillon S, Kupersmith J. The influence of obesity on left ventricular filling and systolic function. Am Heart J 1992;124(3):694-699.

Suk SH, Sacco RL, Boden-Albala B, Cheun JF, Pittman JG, Elkind MS, Paik MC. Abdominal obesity and the risk of ischemic stroke: the Northern Manhattan Stroke Study. Stroke 2003;34:1586-1592.

Sundstrom J, Arnlov J, Stolare K, Lind L. Blood pressure-independent relations of left ventricular structure to the metabolic syndrome and insulin resistance: a population-based study. Heart 2008;94:874-878.

Sundstrom J, Lind L, Nystrom N, Zethelius B, Andren B, Hales CN, Lithell HO. Left ventricular concentric remodeling rather than left ventricular hypertrophy is related to insulin resistance syndrome in elderly men. Circulation 2000;101:2595-2600.

Sutton-Tyrrell K, Newman A, Simonsick EM, Havlik R, Pahor M, Lakatta E, Spurgeon H, Vaitkevicius P and for the Health ABC Investigators. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. Hypertension 2001;38:429–433.

Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. Am J Cardiol 1976;37:7-11.

The Trials of Hypertension Prevention Collaborative Research Group.Effects of weight loss and dietary sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. Arch Intern Med 1997;157:657-667.

Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-3421.

Tomiyama H, Doba N, Kushiro T, Yamashita M, Kanmatsusa K, Kajwara N, Yoshida H, Hinohara S. The relationship of hyperinsulinemic state to left ventricular hypertrophy, microalbuminuria and phsyical fitness in borderline and mild hypertension. Am J Hypertens 1997;10:587-591.

Tsioufis CP, Tsiachris D, Selima MN, Dimitriadis KS, Thomopoulos CG, Tsiliggiris DC, Gennadi AS, Syrseloudis DC, Stefanadi ES, Toutouzas KP, Kallikazaros IE, Stefanadis CI. Impact of waist circumference on cardiac phenotype in hypertensives according to gender. Obesity 2008;17:177-182.

Tsioufis CP, Tsiachris DL, Selima MN, Diminitriadis KS, Thomopoulos CG, Tsiliggiris DC, Gennadi AS, Syrseloudis DC, Stefanadi ES, Toutouzas KP, Kallikazaros IE, Stefanadis CI. Impact of waist circumference on cardiac phenotypes in hypertensives according to gender. Obesity 2009;17:177-182.

Tsotetsi OJ, Woodiwiss AJ, Netjhardt M, Qubu D, Brooksbank R and Norton GR. Attenuation of cardiac failure, dilatation, damage, and detrimental interstitial remodeling without regression of hypertrophy in hypertensive rats. Hypertension. 2001;38:846-851.

Turkbey EB, McClelland RL, Kronmal RA, Burke GL, Bild DE, Tracy RP, Arai AE, Lima JAC, Bluemke DA. The impact of obesity on the left ventricle. The multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol Img 2010;3:266-274.

Urbina EM, Gidding SS, Bao W, Pickoff AS, Berdusis K, Berenson GS. Effect of body size, ponderosity, and blood pressure on left ventricular growth in children and young adults in the bogalusa heart study. Circulation 1995;91:2400-2406.

Utz W, Engeli S, Haufe S, Kast P, Hermsdorf M, Wiesner S, Pofahl M, Traber J, Luft FC, Boschmann M, Schulz-Menger J, Jordan J. Myocardial stetosis, cardiac remodelling and fitness in insulin-sensitive and insulin-resistant obese women. Heart 2011;97:1585-1589.

Velagaleti RS, Gona P, Chuanq ML, Salton CJ, Fox CS, Blease SJ, Yeon SB, Manning WJ, O'Donnell CJ. Relations of insulin resistance and glycemic abnormalities to cardiovascular magnetic resonance measures of cardiac structure and function: the Framingham Heart Study. Circ Cardiovasc Imaging 2010 May;3(3):257-63.

Veliotes DGA, Woodiwiss AJ, Deftereos DAJ, Gray D, Osadchii O, Norton GR. Aldosterone receptor blockade prevents the transition to cardiac pump dysfunction induced by ß-adrenoreceptor activation. Hypertension 2005;45:914-920.

Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Bartoccini C, Santucci A, Santucci C, Porcellati C. Adverse prognostic significantce of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. J Am Coll Cardiol 1995;25:871-878.

Verdecchia P, Reboldi G, Schillaci G, Borgioni C, Ciucci A, Telera MP, Santevsanio F, Porcellati C, Brunetti P. Circulating insulin and insulin growth factor-1 are independent determinants of LVM and geometry in essential hypertension. Circulation.1999;100:1802-1807.

Vetta F, Cicconetti P, Ronzoni S, Rizzo V, Palleschi L, Canarile G, Lupattelli MR, Migliori M, Morelli S, marigliano V. Hyperinsulinaemia, regional adipose tissue distribution and left ventricular mass in normotensive, elederly and obese subjects. Eur Heart J 1998;19:1250-1256.

Wachtell K, Palmieri V, Olsen MH, Gerdts E, Papademetriou V, Nieminen MS, Smith G, Dahlof B, Aurigemma GP, Devereux RB. Change in systolic left ventricular performance after 3 years of antihypertensive treatment: the Losartan Intervention for Endpoint (LIFE) study. Circulation. 2002;106:227-232.

Wada H, Shinjo D, Kameda S, Ono K, Satoh N, Morimoto T, Osakada G, Nakano T, Fujita M, Shimatsu A, Hasegawa K. Transmitral E/A ratio decreases in association with abdominal fat accumulation in patients with impaired glucose tolerance or mild diabetes without left ventricular hypertrophy. Heart Vessels 2010;25:45-50.

Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-1495.

Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 2003;108:977-982.

Wang Y, Huang S, Sah VP, Ross J, Brown JH, Han J, Chien KR. Cardiac muscle cell hypertrophy and apoptosis induced by distinct members of the p38 mitogen-activated protein kinase family. J Biol Chem. 1998;273:2161-2168.

Watanabe K, Sekiya M, Tsuruoka T, Funada J, Kameoka H. Effect of insulin resistance on left ventricular hypertrophy and dysfunction in essential hypertension. J Hypertens 1999;17:1153-1160.

Weber KT, Brilla CG, Janicki JS. Structural remodeling of myocardial collagen in systemic hypertension: Functional consequences and potential therapy. Heart Failure. 1990; 6: 129-137.

Weiss EC, Galuska DA, Kettel Khan L, Gillespie C, Serdula MK. Weight regain in U.S. adults who experienced substantial weight loss, 1999-2002. Am J Prev Med 2007;33:34–40.

Whitlock G, Lweington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. (+157 Collaborators). Body-mass index and cause-specific mortality in 900 000 adults: collaborative analysis of 57 prospective studies. Lancet 2009;373:1083-1096.

Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of obesity are associated with vascular stiffness in young and older adults. Hypertension 2003;42:468–473.

Wilhelmsen L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men: morbidity, risk factors and prognosis. J Intern Med 2001;249:253-261.

Willens HJ, Chakko SC, Byers P, Chirinos JA, Labrador E, Castrillon JC, Lowery MH. Effects of weight loss after gastric bypass on right and left ventricular function assessed by tissue Doppler imaging. Am J Cardiol 2005;95:1521-1524.

Wong CY, Byrne NM, O'Moore-Sullivan T, Hilss AP, Prins JB, Marwick TH. Effect of weight loss due to lifestyle intervention on subclinical cardiovascular dysfunction in obesity (Body mass index >30 kg/m2). Am J Cardiol 2006;98:1593-1598.

Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. Circulation 2004;110:3081-3087.

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

Woodiwiss AJ, Libhaber CD, Majane OHI, Libhaber E, Maseko M, Norton GR. Obesity promotes left ventricular concentric rather than eccentric geometric remodeling and hypertrophy independent of blood pressure. Am J Hypertens 2008; 21:1144-1151.

Woodiwiss AJ, Molebatsi N, Maseko MJ, Libhaber E, Libhaber C, Majane OHI, Paicker J, Dessein P, Brooksbank R, Sareli P, Norton GR. Nurse-recorded auscultatory blood pressure at a single visit predicts target organ changes as well as ambulatory blood pressure. J Hypertens 2009;27:287-297.

Wu CK, Yang CY, Lin JW, Hsieh HJ, Chiu FC, Chen JJ, Lee JK, Huang SW, Li HY, Chiang FT, Chen JJ, Tsai CT. The relationship among central obesity, systemic inflammation and left ventricular diastolic dysfunction as determined by structural equation modeling. Obesity. 2012;20:730-737.

Yusuf S, Hawken S, Ounpuu, S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P Jr, Razak F, Sharma AM, Anand SS; INTERHEART Study Investigators. Obesity and the risk of myocardial

infarction in 27,000 participants from 52 countries: a case-control study, Lancet 2005;366:1640–1649.

Zarich SW, Kowalchuk GJ, McGuire MP, Benotti PN, Mascioli EA, Nesto RW. Left ventricular filling abnormalities in asymptomatic morbid obesity. Am J Cardiol 1991;68:377-81.

Zhou Y-T, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L, Unger RH. Lipotoxic heart disease in obese rats: Implications for human obesity. Proc Nat Acd Sci 2000;97:1784-1789.

Zile MR, Bennett TD, St.John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM, Abraham WT, Smart FW, Stevenson LW, Kueffer FJ, Bourge RC. Transition from chronic compensated to acute decompensated heart failure: Pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation 2008;118:1433-1441.