Cardiac structure and function in obesity: effect of aerobic exercise

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Submitted in accordance with the requirements for the degree of
Doctor of Philosophy

The University of Leeds
School of Biomedical Sciences
Faculty of Biological Sciences

September, 2014

The candidate confirms that the work submitted is his/her own and that appropriate credit has been given where reference has been made to the work of others.

Abstract

Introduction: Obesity is a major risk factor for cardiac related morbidity and mortality particularly in women. Excess body fat induces detrimental LV structural and functional alterations that can potentially be reversed by aerobic exercise training, however the optimal exercise type has not been determined. Firstly the assessment of the impact of excess body fat, on LV structure and function in healthy overweight/obese women was undertaken. Next, the acute LV systolic and diastolic functional responses to heavy-intensity exercise were compared between healthy obese and non-obese women. Finally, the long-term effects of interval and continuous heavy-intensity training on LV structure and function in overweight/obese women were assessed.

Methods: In chapter 4, 85 females were assessed for anthropometric characteristics and LV structure and function then divided into 3 groups; normal weight, overweight and obese. The allometric relationships between each pair of anthropometric and cardiac variables were assessed and the 3 groups were compared for absolute and allometrically scaled LV structural and functional data. In chapter 5, 16 females (8 obese and 8 non-obese) completed a 10-min heavy-intensity exercise session. LV systolic and diastolic function were assessed at rest, 8 min into exercise and 5 min post-exercise and compared between both groups. In chapter 6, 20 overweight/obese females were assessed for LV structure and function before and after completing 12 weeks of either interval or continuous heavy-intensity training. All measures of LV structure and function were assessed by echocardiography.

Results: In chapter 4, excess visceral fat was associated with LV concentric hypertrophy as well as reduced LV diastolic filling velocity, diastolic myocardial velocity and systolic and diastolic myocardial deformation. Fat-free mass (FFM) was identified as the most appropriate scaling variable to normalise for body size without masking the impact of excess fat. In chapter 5, obese woman displayed greater exercise-induced systolic deformation and diastolic filling compared to non-obese women. In chapter 6, both continuous and interval heavy-intensity training resulted in improvement in LV structure, diastolic myocardial velocity and systolic and diastolic myocardial deformation with no difference between both training interventions.

Conclusion: Excess visceral fat is associated with LV concentric hypertrophy and reduced systolic and diastolic function in healthy overweight and obese women. Heavy-intensity exercise enhances LV systolic and diastolic functional response to exercise in overweight/obese women and results in long-term improvements in LV function regardless of exercise type provided it is performed at the heavy-intensity domain.

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Glossary of abbreviations

2D	2-dimensional
2DST	2-dimensional speckle tracking
95%CI	95% confidence interval
A	Late atrial phase diastolic inflow velocity
A2C	Apical 2-chamber
A3C	Apical 3-chamber
A4C	Apical 4-chamber
Am	Late atrial phase diastolic myocardial velocity
ANP	Atrial natiuretic peptide
A-rot	Apical rotation
ASE	American Society of Echocardiography
ATP	Adenosine triphosphate
BIA	Bioelectrical impedance analysis
BM	Body mass
BMI	Body mass index
BP	Blood pressure
B-rot	Basal rotation
BSA	Body surface area
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Cardiac index
CircS	Circumferential strain
CircSRa	Circumferential strain rate during late atrial phase diastole
CircSRe	Circumferential strain rate during early diastole
CircSRs	Circumferential strain rate during systole
CO	Cardiac output
CPX	Cardio-pulmonary exercise
CRF	Cardio-respiratory fitness
CV	Cardiovascular
CVD	Cardiovascular disease
DCT	Deceleration time
E	Early diastolic inflow velocity
EAT	Eapicardial adipose tissue
ECF	Extracellular fluid
EDV	End diastolic volume
EF	Ejection fraction
EFT	Epicardial fat thickness
Em	Early diastolic myocardial velocity
FA	Fatty acid
FFM	Fat-fee mass
FM	Fat mass
FP	Fat percentage
FS	Fractional shortening

HC	Hip circumference
HF	Heart failure
HR	Heart rate
HRR	Heart rate recovery
HT	Height
IBW	Ideal body weight
ICF	Intracellular fluid
IL	Interleukin
IVRT	Isovolumetric relaxation time
IVST	Interventricular septal thickness
IVSTd	Interventricular septal thickness during diastole
Kg	Kilogram
LA	Left atrium
LAD	Left atrial diameter
LongS	Longitudinal strain during systole
LongSRa	Longitudinal strain rate during late atrial phase diastole
LongSRe	Longitudinal strain rate during early diastole
LongSRs	Longitudinal strain rate during systole
LT	Lactate threshold
LV	Left ventricle
LVEDP	Left ventricular end-diastolic pressure
LVH	Left ventricular hypertrophy
LVID	Left ventricular internal diameter
LVIDd	Left ventricular internal diameter during diastole
LVIDs	Left ventricular internal diameter during systole
LVM	Left ventricular mass
LVTor	Left ventricular torsion
MPI	Myocardial performance index
NW	Normal weight
OB	Obese
OW	Overweight
PFR	Peak flow rate
PLAX	Parasternal long axis
PSAX	Parasternal short axis
PWD	Pulse wave Doppler
PWT	Posterior wall thickness
PWTd	Posterior wall thickness during diastole
PWTs	Posterior wall thickness during systole
RadS	Radial strain during systole
RadSRa	Radial strain rate during late atrial phase diastole
RadSRe	Radial strain rate during early diastole
RadSRs	Radial strain rate during early systole
RER	Respiratory exchange ratio
RI	Ramp incremental
ROI	Region of interest
ROS	Reactive oxygen species
RPE	Rate of perceived exertion

RWT	Relative wall thickness
S	Strain
SBP	Systolic blood pressure
SD	Standard deviation
SE	Step exercise
Sm	Systolic myocardial velocity
SR	Strain rate
Sra	Strain rate during late atrial phase diastole
SRe	Strain rate during early diastole
SRs	Strain rate during systole
SV	Stroke volume
SVI	Stroke volume index
TDI	Tissue Doppler imaging
TG	Triglyceride
TNF	Tumour necrosis factor
$Vmax_{LVOT}$	Maximal flow velocity at left ventricular outflow tract
VO_2max	Maximal oxygen consumption
VO_2peak	Peak oxygen consumption
VTI_{LVOT}	Velocity time integral at left ventricular outflow tract
WC	Waist circumference
WHR	Waist to hip ratio
WR	Work rate
WR_{delta}	Delta work rate
WR_{LT}	Work rate at lactate threshold
WR_{peak}	Peak work rate

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Chapter 1 Introduction

Obesity is defined by the WHO as an abnormal or excessive accumulation of fat that may impair health and is commonly classified using the body mass index (BMI) which is the person's weight in kilograms divided by the square of his height in meters (kg/m^2); A BMI ≥ 25 is considered overweight and ≥ 30 obesity (WHO, 2014). Overweight and obesity are major public health concerns and leading causes of global morbidity and mortality. Around 3.4 million adults each year die because of obesity (WHO, 2014, Flegal et al., 2013). The World Health Organisation (WHO) has reported a 10-40% increase in the prevalence of obesity in the majority of European countries over the period between 1990 and 2000. This increase was most drastic in England, where the prevalence of obesity had more than doubled during this period (WHO, 2000).[1] In 2002, national health surveys reported a three-fold increase in the prevalence of obesity in Great Britain since 1980 (Rennie and Jebb, 2005). According to the National Health And Nutrition Examination Survey (NHANES), the prevalence of overweight and obesity in the United States has also been significantly increasing over the past three decades (Flegal et al., 1998) . In 2011, more than two thirds of the American population was reported to be either overweight or obese (Ogden et al., 2014).

Obesity is strongly associated with heart disease. Indeed, obesity is a major risk factor for the development of heart failure (HF) both independently and through its association with co-morbidities such as atherosclerosis, hypertension, dyslipidemia, impaired glucose tolerance and metabolic syndrome (Eckel and Krauss, 1998). Women are particularly at risk of developing cardiovascular disease and approximately 2.4 million women have HF (Jensen et al., 2014). Women present with diastolic HF twice as frequently as men (Jessup, 2003). In 2009, 58.2% of heart failure deaths were women (Jensen et al., 2014). In the Framingham Heart Study population, body mass index (BMI) was shown to increase the population attributable risk of heart failure (HF), with a 7% increase in women and 5% in men for each increment of 1 in BMI (Kenchaiah et al., 2002).

Furthermore, obese women were shown to have double the risk of developing HF compared to non-obese women, whereas obese men only had a 20% increase in the risk compared to non-obese men (Kenchaiah et al., 2002). Furthermore, in a population of 8802 men and women (Dagenais et al., 2005) showed that obesity, and particularly abdominal adiposity, is an independent predictor of all types HF in women but not in men. Indeed, it was shown that for every 0.01 increase in waist-to-hip ratio (WHR) above 0.83, the risk of developing HF increases by 5% in women, whereas in men there was no association between WHR and HF risk (Dagenais et al., 2005).

Earlier autopsy and invasive studies suggested that obesity is associated with eccentric left ventricular hypertrophy, secondary to chronic volume overload, accompanied by diastolic dysfunction which eventually progresses to systolic dysfunction and heart failure (Kaltman and Goldring, 1976, Alexander, 1985). This remained the predominant notion for decades until the development of non-invasive techniques such as echocardiography which enabled researchers to assess LV structure and function in mildly obese normotensive subjects and reporting contradicting findings challenging this classic notion. It was observed by several researchers that mild to moderately obesity is associated with concentric LV remodelling and hypertrophy accompanied by subclinical reduction in both LV systolic and diastolic function. (Alpert, 2001, Alpert and Hashimi, 1993, Danias et al., 2003, Di Bello et al., 2006, Wong and Marwick, 2007b). These structural and functional changes can take years before manifesting themselves clinically, and can eventually result in cardiac failure. In the past, the occurrence of congestive cardiac failure caused entirely by obesity was classically defined as obesity cardiomyopathy. However, with the development of reliable non-invasive techniques capable of detecting subtle myocardial structural and functional deterioration in mild to moderate obesity, Wong *et al*. (2007) suggested that the definition of obesity cardiomyopathy should be extended to include any myocardial disease in obese individuals that cannot be explained by other aetiologies (Wong and Marwick, 2007b).

There has been a lot of disparity with regards to the type of LV morphology and degree of systolic and diastolic dysfunction reported by different studies in association with overweight and obesity. This is partly due to the individual differences between different study populations in the degree of obesity, body composition and fat distribution. Indeed, obesity, defined as a body mass index (BMI > 30 $mg.kg^{-1}$) does not take into account individual

differences in fat and muscle content. Furthermore, several studies have shown that fat distribution, notably abdominal/visceral fat accumulation is a strong determinant of the adverse cardiac outcomes related to obesity. Therefore, a clear distinction between the normal physiological influence of body size and composition and the pathological influence of adipose tissue, taking into account the different fat distribution in the subjects studied, is paramount in the definition of the impact of obesity on LV size, morphology and function. This can only be achieved by normalising cardiac structural and functional variables to body size and composition using allometric scaling procedures (Batterham et al. 1999). Amongst studies comparing cardiac structure and function in obese to non-obese individuals, some researchers normalised cardiac structural and functional variables to body size using ratio-scaling, which assumes a linear relationship between cardiac size and body size resulting in over-correction and errors in the results. Others normalised cardiac variables to body size or composition variables using allometric scaling by raising the body size variable to the power of an allometric exponent. This method was shown to be more accurate, however the exact exponent for each body size or composition variable has also been a point of debate and not clearly defined. Batterham et al. (1999) suggested that in each study, a population specific power exponent offers the most accurate scaling for comparison between individuals. Finally, the choice of body size variable has also been inconsistent in the literature as some studies scaled cardiac size to body mass while others have scaled to body surface area or fat-free mass. Fat-free mass has been identified as the best scaling body size variable. All these inconsistencies would be expected to result in completely different and even at times contradictory findings. Nevertheless, it is generally agree that obesity is associated with an increase in cardiac size and a reduction in systolic and diastolic function. While several studies have explored the allometric relationship between body size and composition and LV size and morphology, the relationship between body size and composition and LV function and whether there is a need to scale functional variables to individual differences in body size and composition has not been clearly defined. Therefore, the first aim of this thesis is to explore the relationship between body size, and composition, notably fat-free mass, on LV size, morphology and systolic and diastolic function using allometric scaling in a population of healthy women.

Several cross-sectional and longitudinal studies have demonstrated that aerobic exercise training is an effective intervention in restoring cardiac

function in obese subjects and reversing the pathological changes induced by obesity (Gondoni et al., 2007, Eriksson et al., 2010, Kosmala et al., 2009). A large number of these studies aimed primarily at reducing weight and therefore designed interventions combining dietary modification with exercise training. While these studies have shown that exercise does indeed maximise weight loss when combined to hypo-caloric diet resulting in improvement in cardiovascular health, it was not clear if these benefits were secondary to a reduction in body fat or the influence of exercise or both. Recent evidence suggests that aerobic exercise training alone improves cardiac structure and function in obese subjects free of comorbid conditions (Morrison et al., 1986, Vogelsang et al., 2008, Ingul et al., 2010, Schuster et al., 2012). Hence, it may be possible to reverse obesity-cardiomyopathy via aerobic exercise training alone without caloric restriction, restoring normal cardiac function and preventing the development of heart failure in obese subjects. This can be particularly of benefit for obese individuals struggling to reduce their weight by caloric restriction.

The exact mode, intensity, and duration of exercise training that achieves the best cardiac outcome in healthy obese subjects is not yet established. Studies that have explored the cardiac benefits of aerobic training on healthy obese subjects, free of cardiovascular morbidities, have used different combinations of intensity, duration and training types. Durations have ranged from as low as 3 weeks to as long as 8 months programmes. While most studies used moderate intensity continuous training programmes (Humphries et al., 2002, Vogelsang et al., 2008, Schrauwen-Hinderling et al., 2010, Sijie et al., 2012) others used high intensity interval training (Sijie et al., 2012, Ingul et al., 2010) and others used a combined resistance and endurance training programme of moderate intensity (Schrauwen-Hinderling et al., 2010, Schuster et al., 2012).

Furthermore, several studies have used different methods for defining the training intensity. While most studies defined it as a percentage of HR_{max} (Ingul et al., 2010, Schrauwen-Hinderling et al., 2010, Schuster et al., 2012, Vogelsang et al., 2008) others used a percentage of VO_{2max} (Mitchell et al., 2002, Baynard et al., 2008, Millen et al., 2014). Shuster et al. designed a training programme aiming at achieving a HR corresponding to the rate of maximal lipid oxidation (Schuster et al., 2012). Finally, some studies did not define a particular intensity and simply encouraged participants to be more active and cycle/walk to and from work (Eriksson et al., 2010). To the best of our knowledge, none of the studies exploring the training-induced cardiac

structural and functional changes have defined training intensity based on lactate threshold (LT).

High-intensity interval training has recently been a topic of increasing interest. Exercise intensity has been shown to be a strong determinant factor in the cardiovascular outcome of aerobic training. According to Wisloff (2007) high-intensity interval training is superior to moderate-intensity continuous training in improving cardiac structure and function in heart failure patients (Mahdiabadi et al., 2013, Wisloff et al., 2007). Very few studies have explored the effects of aerobic interval training on cardiac structure and function in healthy obese subjects. In fact, to our knowledge, only two studies have done so (Ingul et al., 2010, Sijie et al., 2012). Ingul et al. demonstrated that, after 13 weeks of interval training, obese adolescents restored impaired systolic and diastolic cardiac function compared to lean counterparts. Sijie et al. on the other hand, compared both training modes in healthy obese young women and reported a greater increase in SV and EF after high intensity interval training. This study, to our knowledge, is the only study comparing the cardiac effects of interval and continuous training in healthy obese subjects. However, Sijie et al. reported a significant reduction in body fat in both groups after training, which was significantly greater in the interval training group. This, therefore, does not exclude the possibility of weight reduction being a factor in the better cardiac outcome with the interval training group. It is believed that interval training is superior to continuous training in improving cardiac function because of the higher intensities achieved via this training mode. To date, it is not yet known if the repetitive nature of interval training has any additional benefit over continuous training in restoring cardiac structure and function in overweight/obese subjects provided both training modes are in the high intensity domain. The comparison between the influence of work- and intensity-matched interval and continuous training on cardiac structure and function in healthy obese females has not yet been explored. Therefore, the second aim of this thesis is to compare the effects of work-matched heavy-intensity interval and continuous training on LV structure and function in overweight and obese women using novel highly sensitive echocardiographic techniques.

Chapter 2 Literature review

2.1 Evidence on the relationship between obesity and heart disease

Obesity is strongly associated with conditions that affect cardiac structure and function such as diabetes mellitus, hypertension, hyperlipidemia, obstructive sleep apnea and coronary atherosclerosis (Poirier 2006, Caterson 2004), making the independent influence of obesity on the heart difficult to distinguish. Nevertheless, a large body of evidence confirms the independent relationship between obesity and heart disease (Hubert et al., 1983, Chen and Garg, 1999, Dagenais et al., 2005, Kenchaiah et al., 2002).

Hubert et al. examined the cohort of the original Framingham Heart Study population for the development of cardiovascular disease (CVD) over a 26-year follow up period (Hubert et al., 1983). The cohort consisted of 5,209 overweight men and women ranging between 28–62 years of age and free of clinically evident CVD at the beginning of the study. Their results showed that heaviest subjects had a 2-3 fold greater relative risk of developing ischemic heart disease and congestive heart failure after 26 years compared to the leanest ones. This relationship did not change after adjusting for coexisting risk factors including age, systolic BP, serum cholesterol, smoking, glucose tolerance and electrocardiographic left ventricular hypertrophy, indicating an independent association between obesity and heart disease development. Furthermore, the degree of obesity was significantly and positively related to the risk of CVD development.

Several longitudinal follow-up studies showed, later on, similar significant independent relationships between obesity and heart failure development. In the New Haven, Connecticut cohort of the Established Population for Epidemiological Studies of the Elderly Program, consisting of 1749 elderly subjects free of heart disease at baseline, Chen and Garg (1999) reported that, over a 10-year follow-up period, oberweight (BMI ≥ 28 $Kg.m^{-2}$) was found to be an independent predictor of heart failure with a risk ratio of 1.6 (P = 0.04)(Chen and Garg, 1999). Similar findings were reported by He et al. (2001) after conducting the First National Health and Nutrition Examination Survey (NHANS I) Epidemiologic Follow-up Study (He et al., 2001). In this study, He et al. examined the incidence of developing congestive heart

failure (CHF) over an average of 19 years in 13,643 men and women from the NHANES I original cohort, free of overt heart disease at baseline. It was revealed that overweight (BMI ≥ 27.8 or ≥ 27.3 $Kg.m^{-2}$ for men and women respectively) was an independent risk factor for CHF development, with a relative risk of 1.35 ($P < 0.001$).

In the Framingham Heart Study, Kenchaiah et al. (2002) demonstrated that obesity is not only an independent risk factor for the development of heart failure as a continuous variable but also as a categorical variable (normal, 18.5 – 24.9; overweight, 25 – 29.9; obese ≥ 30.0). Indeed, after a follow-up period of 14 years in average, it was shown that the hazard ratios for the development of heart failure for obese women and men were 2.12 and 1.9 respectively compared their non-obese counterparts. Additionally, a graded increase in the risk of heart failure development was shown across the categories of BMI whereby a 7 and 5 percent increase in the risk of heart failure was detected for every increment of 1 $kg.m^{-2}$ in BMI for women and men respectively (Kenchaiah et al., 2002).

Finally, Dagenais et al. (2005) have reported some very interesting findings following their 4.5 year follow-up Heart Outcomes Prevention Evaluation (HOPE) Study. They have demonstrated that people with BMI > 29.8 at baseline had a significant 28% increase in the relative risk of developing CHF when compared with those with BMI < 25.6, a relationship that was no longer significant after waist circumference (WC) or waist to hip ratio (WHR) was added as a covariate. However, different findings were found with abdominal obesity as subjects with WHR > 0.90 had double the risk of developing CHF compared to subjects with WHR < 0.83, with a relative risk of 2.3 ($P < 0.01$), even after including BMI as a covariate. These findings, however were only seen in women (Dagenais et al., 2005). Hence, a large body of evidence suggests that obesity, notably visceral adiposity, is an independent risk factor for the development of heart disease.

2.2 Nature of the relationship between obesity and LV structure and function

Obesity induces structural and functional changes to the heart. Of particular importance, are the structural, morphological and functional changes induced by excess adipose tissue on the left ventricle. The following section will review what is known about the left ventricular structural and functional alterations associated with obesity in the absence of cardiovascular

comorbidities. Firstly, the impact of excess adipose tissue on LV size and morphology will be reviewed, with a particular focus the difference between the physiological impact of body size and composition vs. the pathological influence of excess body fat on LV structure. Next, the impact of uncomplicated obesity on LV systolic and diastolic function will be reviewed. Subsequently, an extensive review of the mechanisms involved in the LV structural and functional alterations in obesity will be carried out.

2.2.1 Obesity and LV structure

Obesity generally induces structural changes to the anatomy of the heart, notably the left ventricle (LV), by causing abnormalities in LV dimension, wall thickness and the geometric pattern resulting from the proportional changes in thickness vs. diameter. It is generally agreed that obesity is associated with LV enlargement, also known a LV hypertrophy (LVH), however there are divergent views regarding the degree of hypertrophy as well as the morphological pattern associated with obesity. This will be reviewed in the below by considering the existing literature on the impact of obesity on LV structure which will be divided into size and morphology and each will be discussed separately starting with LV size. In order to establish the independent impact of excess body fat on LV size, it is imperative to partition out the normal physiological influence of body size and composition using proper scaling techniques. This will be discussed in the following section. This thesis will focus on the left ventricle, and the term LV size will be employed to designate LV mass (LVM) and internal diastolic diameter (LVIDd), whereas the term LV morphology will be employed to designate LVM and relative wall thickness (RWT)

2.2.1.1 The physiological impact of body size on LV size

Regardless of obesity, body size has a natural influence on the size and dimensions of the left ventricle *ie.* an increase in body size will be accompanied by a physiological increase in LV size. Therefore, for comparisons between subjects to be meaningful, it is imperative to normalise LV mass and dimension for individual differences in body size. In the past, cardiac studies have used ratio scaling ie. simply dividing the cardiac size variable, notably LVM, by a body size variable such as body mass (BM), body surface area (BSA) or height (HT). This method has been shown to introduce artefacts and errors in estimating the impact of overweight as it assumes a linear relationship between LVM and body size which was shown not to be the case. Hence, ratio scaling results in

overcorrection for body size in heavy individuals leading to the under-estimation of their LV size.

Allometric scaling is a more accurate method of normalisation for body size and avoids the errors of ratio scaling (Batterham et al., 1999). It consists of dividing the cardiac size variable by the body size variable raised to the power of a scaling exponent. Theoretically, the allometric exponent of each body size variable should follow the theory of geometric similarity ie. LVM (3-dimensional) should relate to BM (3-dimensional) and fat-free mass (FFM, 3-dimensional) to the first power, to BSA (2-dimensional) to the 1.5 power and to HT (one-dimensional) to the 3^{rd} power. Similarly, Left ventricular internal diameter (LVID, one-dimensional) should relate to BM (3-dimensional) and FFM (3-dimensional) to the 0.33 power, to BSA (2-dimensional) to the 0.5 power and to height (one-dimensional) to the first power (Batterham et al., 1999). Multiple scaling studies have explored the allometric relationships between LV size (LVM and LVID) and body size variables in large population samples in order to derive the most powerful associations as well as the specific power exponents for each body size variable (Batterham et al., 1997, Hense et al., 1998, Chantler et al., 2005, Simone et al., 1994, Savage et al., 2008, De Simone et al., 2011). Results from most studies have generally followed closely the theory of geometric similarity in healthy non-obese subjects.

In the context of obesity, in order to properly determine the impact of excess body fat on LV size, it is essential to normalise LVM and LVID for a body size variable that does not incorporate adipose tissue, ie. fat-free mass (FFM) or height (HT). Some studies have suggested that FFM is the most appropriate scaling variable for LVM and LVID and that it should be used rather than height. The FFM allometric exponents for LVM and LVID have been shown to follow the dimensionality theory, ie. not significantly different from 1 and 0.33 respectively and was shown to eliminate gender differences (Daniels et al., 1995, Hense et al., 1998) and give the most accurate results compared with other body size variables (Batterham et al., 1997, Batterham and George, 1998, Hense et al., 1998, Iacobellis et al., 2002). Other studies have recommended indexing LVM for height after showing that it eliminates gender differences and best detects LVH in obese subjects (de Simone et al., 1992, Daniels et al., 1995, Chirinos et al., 2010, De Simone et al., 2011). However, there has been a large disparity in the height exponents reported for LVM by different studies; 2.7 by De Simone, 3 by Daniels and 1.7 by Chirinos (de Simone et al., 1992, Daniels et al., 1995, Chirinos et al., 2010).

De Simone showed that indexing LVM for BSA, $BSA^{1.5}$ or BM erroneously identified LVM as reduced in obese adults whereas this was not the case with $HT^{2.7}$ which reduced the variability in LVM between subjects and best predicted the presence of LVH in overweight/obese subjects. In a study comparing obese men and women, De Simone et al. showed that, although women had significantly lower absolute LVM values than men, after indexing for either FFM and $HT^{2.7}$ this difference was reversed and women had significantly higher indexed LVM than men. This reversal was more pronounced with $HT^{2.7}$. De Simone attributed these results to obesity as women had significantly higher FM than men (De Simone et al., 2011). From these findings, it appears that both FFM and HT are appropriate scaling body size variables in order to remove individual differences in body size without removing the impact of excess adipose tissue as both measures do not incorporate fat unlike BSA and BM. LVM indexed for $HT^{2.7}$ is the most widely used measure of LV size amongst researchers and clinicians as height is easy and simple to measure in comparison to FFM.

With regards to LVIDd, it has not been conventionally indexed to body size and is usually reported as an absolute value. Batterham and Georges (1998) recommended indexing LVIDd for $FFM^{0.33}$ or $BSA^{0.5}$ and advised against indexing it for height as it was associated with the greatest errors (Batterham and George, 1998).

2.2.1.2 The impact of obesity on left ventricular size

Left ventricular (LV) size consists of LV mass (LVM) and internal diastolic diameter (LVIDd). It is well recognised that obesity is associated with a bigger LV size. Autopsy studies have shown that obese individuals have significantly higher LVM and LVIDd than non-obese ones, a phenomenon known as LV hypertrophy (LVH; Smith HL, 1933). This study included morbidly obese subjects that had hypertension, congestive heart failure (CHF) and/or coronary heart disease (CHD).

Echocardiography has enabled researchers to non-invasively assess LV size and morphology in healthy obese subjects free of cardiovascular co-morbidities and establish the independent relationship between obesity and LV size. Left ventricular mass (LVM), as estimated from 2D echocardiography, has been shown to be a powerful predictor of cardiovascular morbidity and mortality (Liao et al., 1997, Stevens et al., 2013).

With regards to the impact of obesity on LV size, the vast majority of cardiology literature has reported significantly higher values for LVM in obese subjects compared to lean controls, including both absolute and indexed LVM. Nevertheless, some studies have reported significantly higher absolute but similar indexed LVM between obese and lean controls (Iacobellis et al., 2002, Saltijeral et al., 2011, Abdelazez, 2014). The reported values for LVM and LVM/$HT^{2.7}$ in overweight/obese subjects in the literature varied from as low as 132.6 ± 30.3 g and 37.5 ± 9 g/$m^{2.7}$ respectively (Chinali et al., 2004) to as high as 234 ± 65 g (Avelar et al., 2007) and 58.85 ± 14.27 g/$m^{2.7}$ respectively (Di Bello et al. 2006). The upper limit of normal for LVM and LVMI as recommended by the American Society of Cardiologist (ASC) is 162 g/$m^{2.7}$ and 44 g/$m^{2.7}$ respectively for women and 224 g/$m^{2.7}$ and 48 g/$m^{2.7}$ respectively for men (Lang et al., 2005).

With regards to LVIDd, older studies reported significantly higher LVID values in obese subjects compared to non-obese controls (Alexander, 1985, Alpert et al., 1995a). These studies included morbidly obese subjects with multiple co-morbidities. More recent echocardiographic studies assessing mild-moderate obesity in subjects free of co-morbodities, have reported disparate findings. While some found significantly higher LVIDd in proportion to LVM in obese compared to lean subjects (Koopman et al., 2012, Saltijeral et al., 2011, Yaseen, 2014), others reported slightly higher LVID in overweight and obese subjects though to a lesser extent than LVM (Peterson et al., 2004, Avelar et al., 2007). Interestingly, others studies reported no significant difference in LVID between obese and controls (Wong et al., 2004, Di Bello et al., 2006, Deng et al., 2010). This discrepancy may be related to the differences in subjects' characteristics in each study in terms of age, degree and duration of obesity, body composition and fat distribution.

2.2.1.3 Obesity and left ventricular morphology

There are two types of LV morphologies: eccentric, indicating an increase in LVIDd in proportion to LV wall thickness with no change in relative wall thickness (RWT), and concentric, indicating an increase in wall thickness that is not paralleled with an increase in LVIDd with a consequent increase in RWT. Relative wall thickness equals the sum of the inter-ventricular septal thickness (IVST) and posterior wall thickness (PWT) divided by LVIDs. A RWT < 0.42 indicates eccentric LV remodelling or hypertrophy, whereas a RWT > 0.42 is concentric. The term remodelling is applied when

LVMI < 51 g/m$^{2.7}$ whereas hypertrophy is when LVMI > 51 g/m$^{2.7}$ (Woodiwiss et al., 2008).

The LV geometric pattern associated with obesity has recently been a topic of debate. The classic description of LV morphology associated with obesity has predominantly been eccentric as demonstrated by earlier studies ((Smith HL, 1933, Nakajima et al., 1985, Messerli, 1982, Lauer et al., 1992, Kono et al., 1994) and supported by recent studies on subjects with isolated obesity (Pascual et al., 2003, Chinali et al., 2006, Tumuklu et al., 2007, Wierzbowska-Drabik et al., 2013, Koopman et al., 2012, Barbosa et al., 2013). This is believed to occur as an adaptation to the large intravascular volume resulting from excess adipose tissue as will be explained later in this chapter. A growing number of studies have challenged this observation by reporting a concentric LV morphology in healthy normotensive obese children and adults (Gutin et al., 1998, Peterson et al., 2004, Mitchell et al., 2002, Wong et al., 2004, Avelar et al., 2007, Woodiwiss et al., 2008, De Simone et al., 2011). The duration and degree of obesity, the body fat content and distribution as well as haemodynamic, hormonal, metabolic and inflammatory factors are believed to be key determinants of LV morphology in uncomplicated obesity as will be discussed later in this chapter.

2.2.2 Obesity and LV systolic function

LV systolic function, or systole, refers to the contraction of the myocardium with subsequent ejection of blood out of the ventricle. It is influenced by preload, afterload and myocardial contractility. Preload refers to ventricular filling and is usually represented by LV end-diastolic volume (EDV) or diameter (LVIDd). LV filling pressure is measured by its surrogate E/Em, where E is early mitral inflow velocity and Em is early myocardial tissue velocity (Ommen et al., 2000). Stretching of the myocardium during diastolic filling results in stronger systolic contraction through the Frank-Starling mechanism. Afterload refers to the tension or stress that develops in the wall of the ventricle during contraction and is measured by its surrogate, end-systolic wall stress (Norton, 2001, Colan et al., 1984). Myocardial contractility refers to excitation-contraction coupling and Ca^{2+} handling within the cardiac myocyte. The echocardiographic assessment of LV systolic function comprises standard echocardiographic parameters, tissue-Doppler imaging (TDI) and two-dimensional speckle tracking (2DST).

2.2.2.1 Standard echocardiography

Ejection fraction (EF) is the most widely used measure of LV systolic function despite having low sensitivity and being strongly affected by HR, preload and afterload (Carabello, 2003). Nevertheless, it remains a popular and reliable indicator of general LV systolic performance. Obesity is associated with an increased intravascular volume and higher CO, in order to meet the high metabolic demands of excess adipose tissue. Higher CO is caused by a higher stroke volume (SV) as HR is usually unchanged in obese subjects. Studies have reported different findings in relation to EF in uncomplicated obesity. The majority of studies reported normal EF and/or FS in healthy obese adults and children, non-significantly different form non-obese controls (Messerli, 1982, Nakajima et al., 1985, Koehler et al., 1989, Stoddard et al., 1992, Veille and Hanson, 1994, Peterson et al., 2004, Tumuklu et al., 2007, Wong et al., 2004, Lorch and Sharkey, 2007, Deng et al., 2010, Orhan et al., 2010, Barbosa et al., 2013, Koopman et al., 2012, Saltijeral et al., 2011, Yaseen, 2014). Nonetheless, a number of studies reported a reduced EF in otherwise healthy moderately obese adults; however two of these studies used radionuclide ventriculography, rather than echocardiography, which may explain the disparity from the echocardiographic studies given the difference in sensitivities in the two methods (Scaglione et al., 1992, Merlino et al., 1994). Karason et al. (1998) showed a reduced EF in healthy obese subjects compared to lean controls, however these subjects were morbidly obese referred for weight-reducing gastroplasty (BMI up to 47 $kg.m^{-2}$) and were shown to have significantly higher systolic BP than controls (Karason et al., 1998). Finally, two studies reported reduced EF in moderately obese otherwise healthy adolescents (Chinali et al., 2006, Ingul et al., 2010). Interestingly, a supernormal EF was observed in obese adults and children by other studies (Di Salvo et al., 2006, Iacobellis et al., 2002, Pascual et al., 2003, Di Bello et al., 2006). This disparity in findings may be related to differences in preload and/or afterload between study groups or differences in subject characteristics such as degree and duration of obesity, body composition and fat content and distribution. Finally, the presence of “hidden” undiagnosed comorbidities such as glucose intolerance, subclinical coronary disease, hypertension and metabolic disorders can sometimes not be excluded by simple history taking and even though these studies reported normal systolic blood pressure (SBP) in their studied subjects, hypertension still may be present as it cannot be excluded by a single reading.

2.2.2.2 Tissue-Doppler imaging (TDI) and two-dimensional speckle tracking (2DST)

Tissue Doppler imaging (TDI) is an echocardiographic technique allowing the quantitative measurement of LV myocardial velocity, deformation and dyssynchrony (Yu et al., 2007). TDI is a relatively more sensitive and less load-dependent measure of LV contractility compared to EF in detecting subclinical global myocardial contractile dysfunction in uncomplicated obesity (Di Bello et al., 2006).

Several studies have reported lower peak systolic myocardial velocity (Sm), both global and regional, in individuals with uncomplicated obesity compared to lean controls, despite both groups displaying similar EF (Di Bello et al., 2006, Peterson et al., 2004, Tumuklu et al., 2007, Wong et al., 2004). Furthermore, Peterson et al. (2004) and Tumuklu et al. (2007) both reported significant inverse correlations between BMI and both global and regional Sm. Studies on obese children reported similar observations of reduced peak Sm only in the LV lateral wall with no change in the septum (Barbosa et al., 2013, Koopman et al., 2012, Saltijeral et al., 2011). This can be due to the tethering effect of the right ventricular overload which is one of the limitations of TDI as it does not distinguish between active and passive movements of the myocardium (Gulati et al., 1996). Two studies reported normal systolic myocardial velocity in obese children (Di Salvo et al., 2006) and adults (Orhan et al., 2010), however they displayed lower myocardial systolic strain and strain rate compared to controls.

Myocardial performance index (MPI), also known as Tei index, is a TDI-derived index of both systolic and diastolic function (Arnlov et al., 2004). It has the advantages of being easy to measure, reproducible, independent of preload, HR and ventricular morphology (Karatzis et al., 2009). Darbik et al. (2010) reported significantly higher Tei index in morbidly obese adults compared to controls denoting systolic and diastolic dysfunction (Wierzbowska-Drabik et al., 2013).

Myocardial deformation, also know as “strain”, is a novel echocardiographic measure of myocardial systolic and diastolic function that can be measured using TDI or 2DST. Strain is defined as the change in length of a segment of the myocardium relative to its resting length (Dandel et al., 2009). Measures of systolic myocardial deformation include strain (S) expressed as a percentage and systolic strain rate (SRs) which is the rate of the deformation (Dandel et al., 2009). Myocardial deformation occurs in three directions during systole: longitudinal shortening, circumferential shortening

and radial thickening. Strain and SRs are novel echocardiographic measurements that allow the assessment of regional as well as global myocardial systolic and diastolic function. They are believed to be less load-dependent and more sensitive than EF and myocardial velocity in detecting subclinical myocardial regional and global dysfunction (Shah and Solomon, 2012). Myocardial deformation can be measured by TDI or 2D speckle tracking (2DST), the latter being more accurate and angle-independent. The TDI-derived S and SRs reported are in the longitudinal direction only due to the angle dependence of this technique (Dandel et al., 2009, Shah and Solomon, 2012). Several studies reported significant impairments in regional and/or global TDI-derived LV longitudinal S and SRs in obese healthy adults and children with preserved EF, FS and occasionally Sm (Di Salvo et al., 2006, Koopman et al., 2012, Orhan et al., 2010, Tumuklu et al., 2007, Wong et al., 2004). Di Salvo argued that the reduced longitudinal deformation in the presence of increased preload is indicative of myocardial contractile dysfunction as longitudinal strain was previously shown to increase with increased preload (Herbots et al., 2004).

Despite the advantages of TDI over conventional echocardiography, it still has its technical limitations. It is angle dependent, does not discriminate between active and passive ventricular motion and may be affected by translational motion of the whole heart (Barbosa et al., 2013, Orhan et al., 2010). Also, TDI-derived myocardial velocity only examines one dimension, namely the long axis of the LV though it has been validated as an index of global LV function.

2.2.2.3 Two-dimensional speckle tracking (2DST)

Two-dimensional Speckle tracking (2DST) is more accurate, sensitive and superior to TDI in assessing myocardial deformation. It is angle independent, has low signal-to-noise ratio, measures deformation in the 3 planes (longitudinal, circumferential and radial), can assess every region of the LV myocardium as well as myocardial twist during systole (Dandel et al., 2009). Studies that used 2DST reported reduced global and regional myocardial deformation in obese subjects with preserved EF, however the directions in which impairment was reported have not been consistent. Some studies reported reduced systolic deformation in the longitudinal and circumferential but not radial directions (Binnetoglu, 2014, Yaseen, 2014) whereas others also reported reduced longitudinal and circumferential together with increased radial systolic strain and strain rate in obese subjects (Saltijeral et al., 2011). Others reported reduced systolic

deformation in the longitudinal and radial but not circumferential directions (Koopman et al., 2012) while others reported reduced circumferential and radial but not longitudinal systolic deformation in obese subjects compared to lean controls (Wierzbowska-Drabik et al., 2013). In a study by Kuznetsova et al. (2008) exploring the distributional characteristics of LV myocardial deformation in a random population, global longitudinal S and global radial SR were found to negatively correlate with WHR and body weight respectively (Kuznetsova et al., 2008).

Left ventricular systolic torsion as well as the rotation of the base (B-rot) and apex (A-rot) can be measured by 2DST giving novel insight LV myocardial contractility. During systole, the LV base rotates clockwise whereas the apex rotates counter-clockwise, resulting from the opposite orientation of the subendocardial and subpericardial fibres and creating a twisting deformation called twist from which torsion is derived (twist normalised to LV length) (Notomi et al., 2005). Few studies have assessed LV rotation and torsion in healthy obese subjects. Deng et al. (2010) reported significantly lower apical and basal rotation, twist and torsion in obese compared to non-obese individuals (Deng et al., 2010). Interestingly, Saltijeral et al. (2012) reported significantly higher LV twist and torsion in obese children compared to controls (Saltijeral et al., 2011).

Two-dimensional speckle tracking has some limitations which may partly explain this discrepancy. It depends on the quality of the 2D image and frame rates which can be challenging especially in obese subjects. Also, it measures the motion of the speckles in the image plane and hence misalignment between the speckles and the ultrasonic plane can lead to out of plane motion (Amundsen et al., 2006). Furthermore, the longitudinal displacement of the base can affect the speckle data obtained in the short-axis view (Geyer et al., 2010). Longitudinal strain measurement has generally been shown to have better reproducibility than radial strain which may also explain the discrepancy in radial data (Geyer et al., 2010).

2.2.3 Obesity and LV diastolic function

LV diastolic function refers to the filling of blood from the left atrium (LA) to the LV across the mitral valve and is dependent on ventricular relaxation, which is an active energy-dependent process, and ventricular compliance, which is a passive process (Nishimura and Tajik, 1997). Diastole consists of 4 phases; (1) isovolumic relaxation which is the short interval between aortic valve closure and mitral valve opening with no change in LV volume, (2)

early diastolic filling phase, which starts by the opening of the mitral valve and is dependent on the pressure differences between the LA and LV, (3) diastasis, which is a short period of little or no filling when the LA and LV pressures become equal, (3) late diastolic filling phase, during which LA contracts to expel the remaining blood into the LV (Little and Downes, 1990). Echocardiographic measures of diastolic function include conventional pulse wave Doppler- (PWD-) derived diastolic transmitral filling patterns, TDI-derived diastolic myocardial velocities and deformation and 2DST-derived diastolic myocardial deformation. The gold standard method for the assessment of LV diastolic function is the measurement of intracardiac pressures as an increase in diastolic filling pressure reflects a reduction in the distensibility of the ventricle. This is an invasive method and therefore has not been frequently employed in healthy obese subjects. E/Em is a validated echocardiographic index of LV filling pressure as will be explained below.

2.2.3.1 Pulse wave Doppler (PWD) echocardiography

Conventional diastolic transmitral LV filling velocities, measured by PWD, include isovolumetric relaxation time (IVRT), early mitral inflow velocity (E), late mitral inflow velocity (A), E/A ratio and deceleration time of early mitral inflow wave (DCT). The patterns of transmitral diastolic filling associated with isolated obesity has been variable in the literature. While some studies reported a reduced E wave and increased A wave (Alpert et al., 1995b, Iacobellis et al., 2002), others reported a reduced E wave and unchanged A wave (Wong et al., 2004, Yaseen, 2014). Several studies, however, reported an increased A wave with an unchanged E wave (Barbosa et al., 2013, Di Bello et al., 2006, Koopman et al., 2012, Orhan et al., 2010, Wierzbowska-Drabik et al., 2013). All these patterns, however, resulted in a reduction in E/A ratio which indicates a degree of diastolic dysfunction in healthy obese subjects. Nonetheless, several studies did not detect any change in neither E nor A waves in individuals with isolated obesity (Abdelazez, 2014, Binnetoglu, 2014, Chinali et al., 2006, Lorch and Sharkey, 2007, Pascual et al., 2003, Peterson et al., 2004, Saltijeral et al., 2011, Di Salvo et al., 2006). Interestingly, one study detected both higher E and A waves in mildly obese adults with no change in E/A ratio (Stoddard et al., 1992). With regards to DCT and IVRT, several studies reported a prolongation in both variables in healthy obese subjects (Alpert et al., 1995a, Binnetoglu, 2014, Di Bello et al., 2006, Di Salvo et al., 2006, Iacobellis et al., 2002, Koopman et al., 2012, Orhan et al., 2010, Karason et al., 1998, Wong et al., 2004) while a few

reported a unchanged DCT and IVRT (Chinali et al., 2006, Lorch and Sharkey, 2007). Despite being reliable and commonly used measures of diastolic function, PWD-derived transmitral filling velocities are influenced by HR, preload and afterload and therefore TDI-derived myocardial diastolic velocities provide less-load dependent and more sensitive option for the detection of subtle diastolic dysfunction (Nishimura and Tajik, 1997, Garcia et al., 1998).

2.2.3.2 Tissue Doppler Imaging

TDI-derived diastolic myocardial velocity include early phase diastolic velocity (Em), late diastolic velocity (Am) and Em/Am ratio. The ratio of E/Em is a recognised surrogate for LV filling pressure and is usually reported as a measure of LV diastolic function. Patterns of diastolic myocardial velocities associated with isolated obesity have been variable in the literature. Some studies reported decreased Em and unchanged (Peterson et al., 2004, Wong et al., 2004, Orhan et al., 2010, Wierzbowska-Drabik et al., 2013) or increased (Di Bello et al., 2006) Am while others reported unchanged Em and increased Am (Barbosa et al., 2013, Koopman et al., 2012, Lorch and Sharkey, 2007). Finally, some reports indicated no change in neither Em nor Am in obese children compared to controls (Binnetoglu, 2014, Saltijeral et al., 2011). The ratio of early transmitral diastolic velocity to early diastolic myocardial velocity (E/Em) is a validated index of LV filling pressure and has been shown to be increased in healthy obese adults and children by several studies (Di Bello et al., 2006, Di Salvo et al., 2006, Wierzbowska-Drabik et al., 2013, Wong et al., 2004, Koopman et al., 2012) however it was reported unchanged by others (Barbosa et al., 2013, Saltijeral et al., 2011).

TDI-derived diastolic deformation include early diastolic strain rate (SRe) and late diastolic strain rate (SRa). These variables are believed to reflect slowing of the rate of relaxation of the LV wall. Fewer studies have assessed TDI-derived diastolic longitudinal deformation in healthy obese subjects. Di Bello et al. (2006) and Koopman et al (2012) reported reduced longitudinal SRe in obese adults and children respectively (Di Bello et al., 2006, Koopman et al., 2012) whereas Lorch and Sharkey (2007) found it similar to controls (Lorch and Sharkey, 2007).

2.2.3.3 Two-dimensional speckle tracking (2DST)

Two-dimensional speckle tracking-derived myocardial diastolic deformation has not been thoroughly investigated in healthy obese subjects. One study

reported reduced circumferential and unchanged longitudinal and radial SRe in morbidly obese subjects (Wierzbowska-Drabik et al., 2013) whereas another study found reduced circumferential and longitudinal but preserved radial SRe in obese subjects compared to controls. This same study reported similar longitudinal, circumferential and radial SRa in both groups (Yaseen, 2014).

From these studies reviewed above, it is evident that isolated obesity is associated with subtle but unfavourable changes in LV structure as well as systolic and diastolic function. The discrepancy between many of these studies could be related to the differences in the characteristics of the subjects enrolled including age, gender, degree and duration of obesity, degree of body fat content, body composition and fat distribution. Obesity is still defined according to BMI which does not separate adipose from muscle tissue, and hence individuals with similar BMIs may not necessarily have the degree of excess adipose tissue vs. muscle tissue.

2.3 Pathophysiology of LV structural and functional changes in obesity

Obesity mediates its detrimental impact on LV structure and function through several mechanisms, as seen above. The abnormal haemodynamic changes associated with obesity are well-established mediators of LV structural remodelling and functional disturbance in obese individuals. Several other factors have been identified and shown to play important roles in the process of obesity-related LV remodelling and systolic and diastolic dysfunction including metabolic, hormonal and inflammatory factors secondary to lipotoxicity and myocardial fibrosis. The following section will review the evidence and theoretical basis of these mechanisms.

2.3.1 Haemodynamic changes

Obesity is associated with an expansion of the intravascular blood volume, due to the high metabolic demands of excessive adipose tissue, rich in vascular network, as well as non-adipose tissue including muscle and skin (Alexander, 1985). This expanded circulatory volume occurs in response to peripheral vasodilatation of capillary and arteriolar network within the adipose tissue and the reduction in peripheral vascular resistance. A subsequent increase in preload on the heart results in increasing LV diastolic filling and stretching of the myocardium resulting in a greater stroke volume via the Frank-Starling mechanism, with no change in HR (Alexander,

1985). It was suggested that renal sodium and water retention also contributes to the high blood volume associated with obesity (Abel et al., 2008). The increased preload and excessive stretching of the myocardium results in LV dilatation and eccentric hypertrophy, ie. chamber dilatation with no change in wall thickness (Alpert et al., 1995a, Abel et al., 2008) which is initially compensatory and not accompanied by functional disturbance. Prolonged exposure to chronic volume overload, LV wall stress increases secondary to chamber dilatation, according to Laplace's law, exerting an increased afterload on the LV and resulting in compensatory thickening of the myocardium, pathological remodelling and eventual concentric hypertrophy with subsequent systolic and diastolic dysfunction and heart failure (Lavie and Messerli, 1986). It is believed that diastolic dysfunction precedes systolic dysfunction in the form of myocardial stiffness and impaired relaxation (Alpert et al., 1995a). Indeed, Di Divitis et al. (1985) reported increased pulmonary vascular resistance, pulmonary capillary wedge pressure, pulmonary artery pressure, right ventricular end-diastolic pressure in morbidly obese subjects. This sequence of pathological events has been the predominant notion for decades before several studies reported concentric LVH in healthy obese subjects which contradicts this notion. Several authors suggested that eccentric LV hypertrophy is in fact a late outcome in the course of obesity secondary to prolonged exposure to volume expansion. It was suggested that early in obesity, in addition to increased preload, an increased afterload is also present secondary to arterial stiffness in the peripheral arterial network with subsequent increased peripheral vascular resistance leading to compensatory LV concentric hypertrophy with subclinical systolic and diastolic dysfunction (Peterson et al., 2004, Binnetoglu, 2014, Di Bello et al., 2006). This was supported by reports of an enlarged aortic diameter and arterial stiffness in the absence of hypertension in obese subjects (Nemes et al., 2008). Iacobellis et al. (1992) however, reported normal LV size and morphology, enlarged aortic root and supernormal ejection fraction in normotensive obese subjects suggesting that the hyperkinetic systole and enlarged aorta are both a result of increased preload rather than afterload and that the earliest impairment in LV function that results from LV hypertrophy is myocardial stiffness which is manifested by impairment of the late phase of diastolic filling (Iacobellis et al., 2002).

Finally, it is now recognise that the haemodynamic changes alone cannot explain the detrimental LV morphological and functional changes associated with obesity and that a combination of several factors such including fatty

infiltration, myocardial fibrosis and hormonal, metabolic and inflammatory changes all play important roles alongside haemodynamic changes (Abel et al., 2008, Alpert, 2001, Wong et al., 2004, Wong and Marwick, 2007a).

2.3.2 Lipotoxicity or myocardial steatosis

Obesity is associated with a high fatty acid (FA) uptake and conversion into triglyceride (TG) droplets that accumulate in the cytosol of cardiac myocytes. This accumulation of fat in cardiac myocytes, is termed lipotoxicity or myocardial steatosis (Sacks and Fain, 2007, Wong and Marwick, 2007a). The high fatty acid uptake is secondary to high circulating free FAs as well as direct fatty infiltration from the epicardial adipose tissue (EAT) after excessive fat accumulation (Sacks and Fain, 2007). EAT is the visceral fat depot of the heart. It is normally located along the atrio-ventricular and inter-ventricular grooves and as adipose tissue accumulates with obesity it spreads to cover the surface of the ventricles (Figure 2.1). It is characterised by having a strong capacity to freely uptake and release free FAs. In the absence of obesity, it is believed to protect the heart against exposure to high levels of free FAs and provide the heart with energy needs. However, as obesity progresses and accumulation of fat in the EAT increases it releases FAs directly into the myocardium which, together with the vascular delivery of free FAs, causes decrease in the FA oxidative capacity of cardiac myocytes which can no longer cope with the FA delivery, leading to cellular lipid accumulation, lipotoxicity and myocardial steatosis (Sacks and Fain, 2007). In a study by Kankaanpaa et al. (2006) an increase in myocardial triglyceride content, detected by spectroscopy, was strongly associated with EAT mass, WHR free, FA levels and LVM (Kankaanpaa et al., 2006). Myocardial steatosis and lipotoxicity results in metabolic disturbances within the cardiac myocytes, notably mitochondrial disturbance and alterations in substrate utilization as well as release of pro-inflammatory cytokines, myocardial fibrosis and apoptosis with subsequent contractile disfunction, as will be explained below.

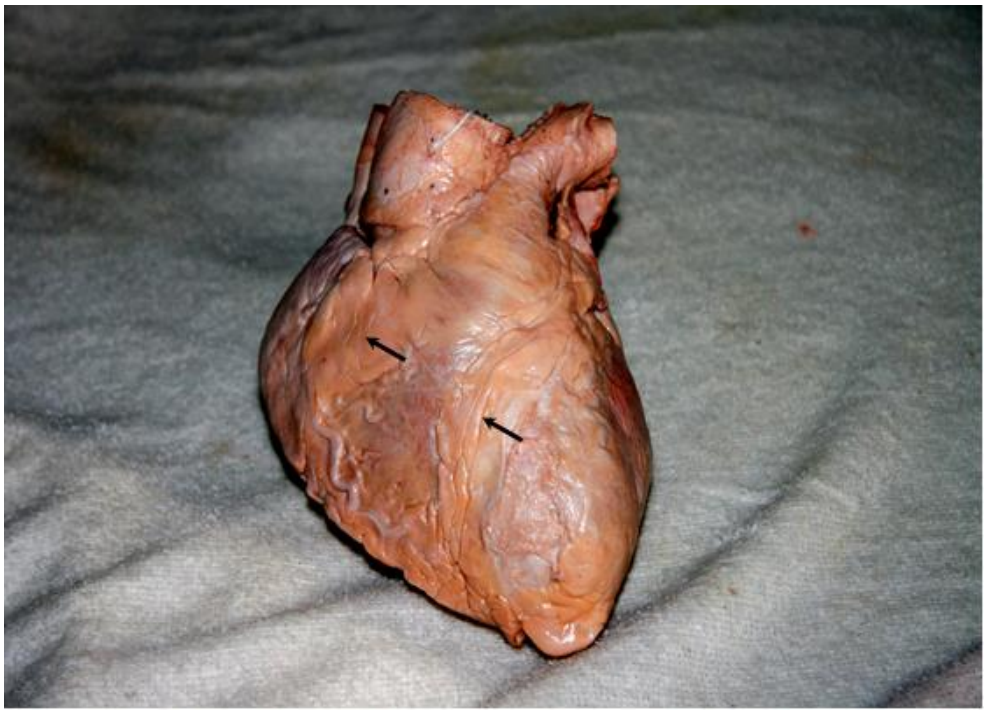

Figure 2. 1 Macroscopic appearance of epicardial adipose tissue. Epicardial adipose tissue tends to be distributed along the atrio-ventricular and inter-ventricular grooves (black arrows), extending to cover the ventricular surface as adipose tissue accumulates.

2.3.3 Cellular metabolic disturbance

Obesity is associated with metabolic disturbances within the cardiac myocytes. Animal studies have shown detrimental alterations in substrate utilization in in cardiac myocytes isolated from obese mice models. This consisted of an increase in FA oxidation and a reciprocal decrease in glucose oxidation and this was observed prior to detectable changes in cardiac function on isolated hearts (Buchanan et al., 2005). These changes are believed to result from increased FA delivery to cardiac myocytes, impaired insulin signaling and activation of transcriptional pathways resulting in increased expression of genes involved in FA import (Abel et al., 2008).. Additionally, obesity is associated with mitochondrial dysfunction whereby an increase in mitochondrial oxygen consumption is accompanied by a decrease in ATP production, a condition termed mitochondrial uncoupling. This further increases FA utilization and subsequent release of pro-inflammatory cytokines, fibrosis, apoptosis and myocardial contractile dysfunction (Abel et al., 2008).

2.3.4 Inflammation

Myocardial steatosis and lipotoxicity result in intracellular accumulation of toxic byproducts of FA oxidation, increased oxidative stress within cardiac myocytes with resultant increased production of reactive oxygen species (ROS) and pro-inflammatory cytokines including interleukin-6 (IL-6), atrial natriuretic peptide (ANP) and tumour necrosis factor (TNF). This results in subsequent cellular damage, myocardial fibrosis and dysfunction (Abel et al., 2008, Wong and Marwick, 2007b). Furthermore, EAT accumulation results in paracrine release of pro-inflammatory adipokines including TNF-alpha, MCP-1, IL-1β, IL-6, IL-8 and others resulting in inflammation, fibrosis, apoptosis, disturbance in signalling pathways and subsequent contractile dysfunction (Sacks and Fain, 2007).

2.3.5 Hormonal alterations

Obesity is associated with several hormonal alterations including insulin resistance, leptin insensitivity and reduced adiponectin expression (Wong and Marwick, 2007b). Excess adipose tissue causes impaired intracellular insulin signaling in the heart as shown by animal studies. Insulin resistance is believed to be responsible for detrimental outcomes in cardiac myocytes via several mechanisms. Insulin resistance reduces glucose uptake and increase FA oxidation, change cardiac myocyte gene expression, promote cellular apoptosis and dysfunction and increase myocardial susceptibility to injury when exposed to pressure overload or chronic adrenergic stimulation (Abel et al., 2008, Wong and Marwick, 2007b). Furthermore, insulin resistance can result in compensatory hyperinsulinema and binding of insulin to insulin-like growth factor-1 receptors on cardiac myocytes resulting in their proliferation and differentiation which could explain the strong association between insulin resistance and LV hypertrophy (Abel et al., 2008). Furthermore, hyperinsulinema leads to an increase in angiotensinogen level and subsequently angiotensin II which is a potent growth factor for cardiac myocytes promoting cell proliferation, hypertrophy, apoptosis and fibrosis and leading to myocardial dysfunction (Wong and Marwick, 2007b). Several studies reported a strong association between fasting insulin level and diastolic dysfunction suggesting an action of insulin on LV relaxation (Iacobellis et al., 2002, Wong et al., 2004, Mureddu et al., 1998). Moreddu suggested that insulin resistance can cause impairment of myocardial actin-myosin cross-links due to lack of Ca^{2+} re-uptake from the sarcoplasmic reticulum (Mureddu et al., 1998). Furthermore, there is a strong association between hyperinsulinema, insulin growth factor-1 (IGF-1)

and left ventricular hypertrophy in obese subjects (Ohya et al., 1996) and concentric remodelling suggesting that insulin resistance plays a role in LV concentric hypertrophy. Additionally, Di Bello et al. (2006) showed a strong correlation between insulin resistance, LVMI and myocardial systolic and diastolic deformation and velocity, further supporting that insulin resistance plays a role in LV hypertrophy and dysfunction and increased myocardial collagen content in obesity. Kosmala et al. (2012) showed significant inverse correlations between insulin resistance and systolic and diastolic deformation and velocity further suggesting an impact of insulin resistance on LV dysfunction (Kosmala et al., 2009). Indeed, Di Bello et al. (2006) reported a strong association between insulin resistance and altered myocardial reflectivity seen on integrated backscatter indicating increased myocardial fibrosis and/or steatosis and lipoapoptosis in severly obese subjects (Di Bello et al., 2006). Obesity is also associated with leptin-resistance and reduced adiponectin expression which induces apoptosis and results in LV contractile dysfunction.

2.4 Impact of aerobic exercise training on LV structure and function in obesity

The benefits of aerobic training on cardiovascular function are well-established (Blomqvist and Saltin, 1983). A large body of evidence show that aerobic training induces favourable cardiac structural and functional adaptations resulting in improvement of cardiac performance in healthy individuals as well as cardiac patients (Blomqvist and Saltin, 1983, Erbs et al., 2003, Giannuzzi et al., 2003, Levy et al., 1993, Shapiro and Smith, 1983, Smart et al., 2006, Smart et al., 2007, Spina et al., 1992a, Spina et al., 1992b). Of particular importance, are the LV structural and functional adaptations to aerobic training in obese individuals. Recent evidence suggest that aerobic training alone can reverse obesity-mediated LV pathological remodelling and restore normal systolic and diastolic function in otherwise healthy obese individuals without the need to reduce body weight through caloric restriction (Morrison et al., 1986, Vogelsang et al., 2008, Ingul et al., 2010, Schuster et al., 2012). This can be of particular benefit in obese individuals who struggle or are unable to reduce their body weights, protecting them from the detrimental outcomes of obesity on the heart, slowing down or reversing the pathological development of obesity cardiomyopathy and eventual heart failure. The following section will review what is known about LV structural and functional adaptations to aerobic

exercise in healthy obese individuals. First, the systolic and diastolic functional response to exercise in obese individuals will be reviewed. Next, the structural, morphological and functional adaptations to long term aerobic training in healthy obese individuals will be reviewed. Finally, the impact of exercise intensity and benefits of aerobic interval training will be outlined.

2.4.1 LV functional response to exercise in obesity

Physical exercise subjects the heart to a form of physiological and metabolic stress and therefore, in obese individuals, extra effort is required from the heart to meet the high metabolic demands of the working muscles in addition to the excess adipose tissue. The normal physiological cardiovascular response to aerobic exercise consists of haemodynamic changes paralleled by LV functional alterations in order to meet the oxygen demands of the working muscles. During aerobic exercise, peripheral vasodilatation and the pumping action of the working skeletal muscles result in expansion of central blood volume with a resultant increase in LV venous return. Despite the increased venous return, the LV diastolic filling volume and end-diastolic diameter remain constant, as a protective mechanism against stretch-induced rise in LV wall stress according to Laplace's law (Rowland, 2008). A decrease in LV end-systolic diameter and volume, together with a rise in heart rate can result in increased stroke volume and cardiac output. The reduced LV end-systolic diameter is achieved by an enhanced LV systolic contractile performance, represented as a greater speed, force and acceleration of contraction in a shorter time. (Rowland, 2008). This is manifested on echocardiography as decreased ejection time, increased ejection fraction, fractional shortening, systolic blood flow velocity and systolic myocardial velocity, circumferential and longitudinal shortening and torsion (Rowland, 2008). With regards to LV diastolic function during exercise, it parallels the systolic functional response with shortening of diastolic time intervals and increased diastolic filling rates, myocardial relaxation, circumferential and longitudinal elongation and LV diastolic untwisting (Rowland, 2008). All these changes progressively increase with increasing exercise intensity, with the exception of stroke volume that only rises initially then remains stable.

Within the context of obesity, studying the LV response to exercise in obese individuals can be viewed, on one hand, as an additional diagnostic tool to detect subtle reductions in LV systolic and diastolic contractile performance that are only detectable under the additional stress of exercise on the heart. On the other hand, it allows the understanding of the long-term exercise-

induced LV structural and functional adaptations in obese subjects and whether their response to exercise differs from non-obese individuals. The following section will review what is known about the LV systolic and diastolic functional response to aerobic exercise in healthy obese individuals..

2.4.1.1 LV systolic function during exercise in obesity

Studies that have explored cardiac response to exercise in healthy obese subjects are very limited and have reported somewhat disparate findings. In one of the earliest studies, Alpert et al. (1989) assessed the EF response to maximal exercise in 23 morbidly obese (≥ twice Ideal Body Weight; IBW) otherwise healthy men and women, using radionuclide ventriculography at the end of an incremental supine cycling session (Alpert et al., 1989). The cohort was divided into 2 groups according to the presence or absence of LVH. It was found that, despite both groups having similar resting EF, a significant (11 ± 10%) increase in EF at peak exercise was detected in the group with normal LVM whereas no significant change was seen in the LVH group. Both groups had similar magnitudes of change in HR and mean BP (MBP) from rest to peak exercise. Additionally, a strong significant correlation was reported between %IBW and LVM which inversely correlated with exercise-delta EF. Alpert concluded that the degree of obesity determines the degree of LVH and consequently the EF response to exercise (Alpert et al., 1989). Licata (Licata et al., 1992) confirmed and extended these observations by assessing the impact of both the degree and duration of obesity on the EF response to maximal exercise in 29 overweight and moderately obese adults using radionuclide ventriculography. A significant (>5%) increase in EF at maximal exercise was shown only in the overweight group with no significant change in the moderately obese group. On subdividing the groups according to the duration of obesity, only the overweight subjects that had been overweight for less than 10 years showed a significant increase in EF at maximal exercise whereas the moderately obese group did not show any significant change in EF regardless of the duration of obesity. Both groups, however had non-significantly different LVM and LVMI. Exercise-delta EF significantly and negatively correlated with the duration of obesity but not BMI or resting EF (Licata et al., 1992). Licata concluded that the degree and duration of obesity are useful predictors of LV systolic functional reserve in subjects with normal LVM. These two studies that early in obesity and before the development of LVH, overweight/obese individuals display enhanced LV

systolic function during exercise, a response that is lost as obesity progresses further. Reports from Ferraro et al. (1996) also showed poor LV systolic response to exercise in severely obese adults as, in addition to having significantly lower EF at rest, they showed no change in EF during submaximal supine cycling whereas a significant (~5%) increase was detected in the control group (Ferraro et al., 1996). Sasso et al. (2005) extended these findings by showing that, despite having a significantly higher EF at rest, overweight and moderately obese adults displayed significantly lower exercise-induced increase in EF during supine cycling at 75 W load compared to lean controls (Sasso et al., 2005). Furthermore, the exercise-induced increase in EF was significantly higher during insulin infusion in both groups. Sasso concluded that, even though overweight/obese subjects displayed higher resting EF than lean controls, possibly reflecting an initial compensatory increase in systolic function, exercise revealed a reduction in systolic function which is likely related to insulin resistance (Sasso et al., 2005). This conclusion, however needs to be validated by more sensitive, less load-dependent measures of systolic function such as TDI and 2DST-derived myocardial velocity, deformation and torsion, as EF despite being a reliable indicator of LV general systolic performance, it does not assess myocardial contractility and is highly influenced on changes in HR, preload and afterload.

Other studies have compared obese and lean subjects with regards to their cardiac output (CO), cardiac index (CI; CO/BSA), stroke volume (SV) and stroke volume index (SVI) responses to exercise. Salvadori et al. (1999) compared cardiac performance of moderately to severely obese subjects at rest and during upright cycling at 40 W and 70 W to non-obese controls (Salvadori et al., 1999). Obese subjects had similar resting but higher exercise CO compared to lean controls, however they had similar resting but lower exercise CI at 40 W and 70 W compared to lean counterparts. A significant inverse correlation was found between CI and work rates in both groups with a significantly lower slope in the obese group than controls. Salvadori concluded that cardiac performance in obese subjects, although similar to non-obese subjects at rest, is less efficient during progressive exercise. Giordano et al. (2003) also reported significantly reduced peak CI in obese children, compared to controls despite both groups displaying similar resting CI (Giordano et al., 2003).

These findings were challenged by (Rowland et al., 2003) who reported higher resting and exercise SV and CO throughout an incremental upright

cycling session until maximal exercise in moderately obese young girls compared to lean counterparts, and maximal CI was not significantly different. Rowland concluded that excess body fat does not reduce cardiac functional capacity in moderately obese adolescent females and that on the contrary significantly greater SV and CO were manifested at peak exercise (Rowland et al., 2003). Interestingly, Vella et al. (2009) showed significantly higher resting and exercise absolute CO and SV as well as EF in overweight and moderately obese adults during upright cycling at 50, 75 and 100 W compared to controls (Vella et al., 2009). In fact significantly higher exercise-induced change in SV and EF were detected in the obese group compared to controls. In another study, Vella et al. (2011) assessed cardiac performance throughout an incremental upright cycling session until exhaustion and reported that, in moderately obese adults resting and maximal CI and SVI were non-significantly different from controls, however they were significantly higher throughout the incremental exercise session. With regards to EF, it was significantly lower in the obese group at rest and throughout the incremental exercise but reached similar values to the control group at submaximal and maximal exercise.

Ingul et al. (2010) were the first to assess TDI-derived LV myocardial velocity and deformation in addition to haemodynamic parameters during exercise in obese subjects (Ingul et al., 2010). This was carried out before and after a 3 months heavy-intensity interval training programme. In comparison to lean controls, the obese group displayed significantly lower systolic function both at rest and during upright cycling at 100 W compared to lean controls, represented as lower mitral annulus excursion (MAE), velocity time integral of the LV outflow tract (VTI_{LVOT}), maximum velocity of LVOT ($Vmax_{LVOT}$), peak systolic myocardial velocity (Sm), global strain and systolic strain rate. After the 3-months exercise intervention, with the exception of $Vmax_{LVOT}$ and Sm, systolic function increased in the obese group to similar values as the lean controls both at rest and during exercise without any weight reduction. At rest, $Vmax_{LVOT}$ was similar in both groups, however it was significantly lower in the obese group during exercise compared to controls. The opposite was true with regards to Sm as it was significantly lower at rest but increased to become similar to the control group during exercise. This study, however did not compare the exercise-deltas of systolic function between both groups.

A recent study by Shuster et al. (2012) assessed global and regional LV systolic performance using TDI echocardiography in first and second degree

obese young boys throughout an incremental supine cycling session until exhaustion. It was shown that the obese group had significantly higher absolute SV and CO at rest, throughout the incremental exercise and at maximal exercise compared to controls. However, CI and SVI were non-significantly different in both groups neither at rest nor throughout exercise. As for FS and Sm, both mild and moderately obese children displayed non-significantly different values at rest and throughout the incremental exercise, In moderately obese children both measures levelled off at submaximal and maximal exercise to significantly lower levels compared to both lean and mildly obese children. This further confirms the presence of subtle systolic dysfunction in obese individuals that could only be detected during near maximal exercise.

In conclusion, it appears that in early, mild/moderate obesity, before pathological LVH, LV systolic functional response to exercise is similar, if not superior, to non-obese individuals with some evidence of reduced functional capacity at maximal exercise only. More severely obese individuals appear to display reduced cardiac systolic capacity during exercise. The existing evidence is still not conclusive enough as very few studies assessed LV functional response to exercise using novel techniques that give a more sensitive and load-independent indication of systolic function. Furthermore, the discrepancy between studies could be related to the different imaging techniques employed, mode of exercise (supine, semi-supine or upright) and intensity used. Also, the assessment of the pattern of change in LV performance throughout an entire incremental exercise session gives more information than the assessments at fixed time points. For instance, Vella et al. (2009) showed that SV was similar in both obese and non-obese groups at rest and maximal exercise, however it was significantly higher in the obese group throughout the incremental exercise session (Vella et al., 2009). Finally, metabolic and hormonal factors might also play an important role such as insulin resistance was shown by (Sasso et al., 2005). This is of particular relevance when defining the type of obesity ie. peripheral vs. visceral fat distribution.

2.4.1.2 LV diastolic function during exercise in obesity

Fewer studies have assessed LV diastolic performance during exercise in healthy obese individuals. In an early study, Alexander and Peterson (1972) reported abnormally elevated LV end diastolic pressure (LVEDP) during supine cycling, measured by intracardiac catheterization, in nine morbidly obese adults (> twice IBW) (Alexander and Peterson, 1972). This persisted

even after profound weight loss. The authors attributed this high LVEDP to LV diastolic dysfunction secondary to decreased compliance associated with myocardial hypertrophy. Consistent with these results, Ingul et al. (2010) reported significantly higher E/Em ratio, an well-validated echocardiographic surrogate marker of LVEDP, and lower Em, both at rest and during upright cycling at 100 W, in moderately obese compared to lean adolescents (Ingul et al., 2010). Interestingly, after the obese group completed a 3 months heavy-intensity interval training programme, both E/Em ratio and Em decreased to similar values as non-obese controls both at rest and during exercise without any accompanying weight reduction. Sasso et al. (2005) compared peak flow rate (PFR), a measure of LV diastolic function, using angioscinthigraphy, in overweight and obese adults compared to lean controls at rest and during supine cycling at 75 W (Sasso et al., 2005). Obese subjects had significantly lower resting and exercise PFR, which did not change during insulin infusion suggesting that LV diastolic dysfunction in obesity is unlikely related to insulin resistance. Schuster et al. (2012) compared LV performance during an incremental exercise session in the semi-supine position in mild and moderately obese children and non-obese controls on (Schuster et al., 2012). All 3 groups showed similar E velocity at rest, incremental and maximal exercise. At all stages of assessment, the mildly obese children showed significantly higher Em than controls whereas the moderately obese children showed significantly lower Em than controls. Shuster suggested that early in lower degrees of obesity, a compensatory increase in diastolic function is seen during exercise in order to optimise increased diastolic filling, however, with more severe degrees of obesity, eventual diastolic dysfunction occurs. This study also reiterates the importance of using sensitive and relatively load-independent techniques such as TDI in order to detect subtle changes in function not detected by standard PWD.

As shown by the above studies, obese subjects do manifest a reduced LV diastolic function both at rest and during exercise compared to non-obese counterparts, however no comparison has been made with regards to the amount of change during exercise. Mild to moderate degrees of obesity appear to have compensatory increase in diastolic function both at rest and during aerobic exercise, however, more studies are required for this conclusion to be validated.

In conclusion, to date an accurate comparison LV response to exercise in obese and non-obese healthy individuals using sensitive, load-independent

echocardiographic techniques are lacking. More importantly, the proper matching of participants for exercise intensity domain is crucial. None of the previous studies reviewed above have accounted for individual differences in lactate threshold (LT) and VO_{2max}, alternatively participants exercised at fixed work rates and would have been exercising at different intensities from each other. This can potentially result in errors in the conclusion as the heart would be subjected to different intensities within participants of the same study or participants in-between studies.

2.4.2 LV structural adaptation to aerobic exercise training in obesity

Generally, long-term aerobic exercise training is known to result in significant alterations in LV structure, consisting of eccentric hypertrophy *ie.* increase in chamber diameter and wall thickness, accompanied by systolic and diastolic adaptations. This process is called exercise-induced cardiac remodelling (Weiner and Baggish, 2012). In addition to the type of exercise and the duration and intensity of training, the extent of exercise-induced cardiac remodelling is also determined by gender, race and genetic factors (Weiner and Baggish, 2012). In this section, the structural and functional LV adaptations to long-term aerobic exercise training in obese individuals will be reviewed. It should be noted that the following review will only include longitudinal studies involving healthy overweight and/or obese individuals free of any cardiovascular co-morbidities. Additionally, only studies involving aerobic endurance training in the form of walking, running, cycling or rowing will be considered and studies including dietary interventions will be excluded.

2.4.2.1 Impact of aerobic training on LV structure in obesity

Reports from longitudinal studies exploring the influence of aerobic training on measures of LV size and morphology in healthy normotensive obese subjects have been somewhat inconsistent. Several studies showed no significant change in either LV size or morphology following aerobic training (Baynard et al., 2008, Eriksson et al., 2010, Millen et al., 2014, Mitchell et al., 2002, Stewart et al., 2006). These studies involved overweight and/or moderately obese adults and used a variety of training durations and intensities including 6 months low-intensity training (Eriksson et al., 2010), 6 months mixed moderate-intensity continuous endurance and strength training (Stewart et al., 2006, 6 weeks moderate-intensity continuous or heavy-intensity interval training (Millen et al., 2014) and 10 days heavy-

intensity interval training. Mitchell et al. (2002) reported a slight increase in diastolic LV posterior wall thickness (PWTd), diastolic interventricular septum thickness (IVSTd) and diastolic LV internal diameter (LVIDd) after 8 months moderate-intensity training in obese adolescents but no change in LVM or LVMI was observed (Mitchell et al., 2002). Two studies reported a post-training increase in LVM following aerobic training. Humphries et al. (2002) reported an increase in absolute LVM, but not LVMI, with no change in RWT in children after 4 months of aerobic training at a HR > 150 bpm (Humphries et al., 2002). Furthermore, an association between the training-induced increase in LVM and decrease in heart rate reactivity was reported, indicating that those that improve the most in fitness are more likely to increase LVM. It was noted that a significant decrease in fat mass and increase in fat-free mass was reported post-training. Vogelsang et al. (2008) reported a post-training increase in LVM and LV EDV in 10 moderately obese adults after 8 weeks of moderate intensity rowing, attributing these changes to the Frank-Starling mechanism (Vogelsang et al., 2008). Vogelsang argued that increased EDV indicates an increased preload in response to training that has possibly increased the chamber diameter, stretching its walls and causing reflex eccentric hypertrophy to diminish wall stress (Vogelsang et al., 2008). It should be noted that this study used MRI which is more sensitive than echocardiography. Finally, only one study reported a reduction in LVM with no change in RWT or EDV following 8 weeks of low-intensity aerobic training in 10 moderately obese adults (Schuster et al., 2012). It was noted that the subjects involved had severe concentric LVH (average LVM = 234.6 ± 16.9 g) before training which may explain the exercise-induced reverse remodelling via reduction in LVM as opposed to the increase or no change in LVM in the previously mentioned studies in which LVM values were all within normal range before interventions. The training intensities and durations varied greatly among these studies which may partly explain the discrepant results. Also, changes in body composition could play a role as some of these studies reported a reduction in fat percentage following training whereas others reported an increase in muscle mass.

2.4.2.2 Impact of aerobic training on LV systolic function in obesity

With regards to standrard echocardiographic measures of systolic function, reports have been disparate. Vogelsang et al. (2008) reported a post-training increase in EDV and SV with no change in EF, measured by MRI, in

10 moderately obese adults after 8 weeks of moderate intensity training and (Vogelsang et al., 2008) whereas Sijie et al. (2012) reported an increase in EF and a reduction in resting HR in overweight women after 12 weeks of either heavy-intensity interval training or moderate intensity continuous training (Sijie et al., 2012). Two studies (Ingul et al., 2010, Schrauwen-Hinderling et al., 2010) reported a post-training increase in both SV and EF following 13 weeks of heavy intensity interval training and 12 weeks of combined moderate intensity endurance and resistance training respectively. Eriksson et al. (2010) reported a slight increase in mitral annular excursion (MAE) by standard M-mode echocardiography with no change in FS following 6 months low-intensity training in moderately obese women, whereas Ingul et al. (2010) reported an increase in both these measures following 13 weeks heavy-intensity interval training in obese adolescents.

With regards to LV myocardial velocity and deformation, one study reported an increase in systolic TDI-derived myocardial velocity (Sm), longitudinal strain (LongS) and longitudinal systolic strain rate (LongSRs) in addition to standard measures of LV systolic function including SV, EF, MAE and $LVOT_{VTI}$ following 13 weeks of heavy-intensity interval training in obese adolescents (Ingul et al. 2010), whereas another study reported a post-training increase in TDI-derived LongS and LongSRs with no change in EF, SV, CO or Sm after 8 weeks of low-intensity aerobing training in moderately obese adult men (Schuster et al., 2011). Schuster also reported a decrease in systolic intraventricular dysynchrony following training. Both these studies also reported a post-training reduction in body fat content, in particular visceral fat.

Finally, some studies failed to detect any changes in LV systolic function following aerobic training in healthy obese normotensive subjects. Mitchell et al. (2002) reported no change in either LV structure or mid-wall fractional shortening (MFS) in obese adolescents following 8 months of moderate or heavy-intensity aerobic training (Mitchell et al., 2002). Similarly, Humphries et al. (2002) showed no training-induced change in CO or MFS despite an increase in LVM following 4 months of aerobic training at a HR > 150 bpm in obese children (Humphries et al., 2002). Baynard et al. (2008) showed that 10 days of heavy-intensity aerobic training did not result in any change in LV structure of MFS in obese adults with or without metabolic syndrome (Baynard et al., 2008). Finally, Millen et al. (2014) reported no training-induced change in EF, MFS or Sm in overweight and obese adults after 6

weeks of either moderate intensity continuous or heavy-intensity interval training (Millen et al., 2014).

2.4.2.3 Impact of aerobic training on LV diastolic function in obesity

Most studies that have used standard pulse wave Doppler echocardiography to assess LV diastolic filling velocities (E, A and E/A ratio) in healthy obese subjects following aerobic training found no significant change after training. Two studies reported significant reductions in DCT and IVRT following 13 weeks of heavy-intensity interval training in obese adolescents (Ingul et al., 2010) and 8 weeks of low-intensity training in 10 obese adults (Schuster et al., 2011). With regards to diastolic myocardial velocity, they reported an increase in TDI-derived Em post-training whereas Millen et al. (2014) reported no change in either LV diastolic filling velocities or Em after 6 weeks of either moderate or heavy-intensity training in overweight and obese adults (Millen et al., 2014). One study assessed diastolic LV dyssynchrony using TDI and diastolic myocardial deformation using 2D speckle tracking echocardiography and reported a significant increase in both diastolic dyssynchrony and SRe in healthy obese adults after 8 weeks of low-intensity aerobic training (Schuster et al., 2011). Despite a lack of training effect on diastolic function, Stewart et al. (2005) showed a negative correlation between the training-induced increase in both E wave and E/A ratio and the decrease in abdominal fat and insulin level (Stewart et al., 2005). Additionally, in a stepwise regression model, the reductions in abdominal fat and insulin accounted for 7% and 5% respectively of the variance of E wave. Subjects in this study were 51 overweight to mildly obese men and women (mean age 63.6 ± 5.7 years) and training involved 26 weeks of 15 min resistance training followed by 45 min of moderate-intensity aerobic training. Finally, Eriksson et al. (2010) reported no significant change in diastolic function following 6 months low intensity training in mildly obese adults, neither did Millen et al. (2014) following 6 weeks of either moderate intensity continuous or heavy-intensity interval training.

2.4.3 Factors determining aerobic training effects on LV structure and function in obese subjects

The disparity between studies with regards to LV structural and functional adaptation to aerobic exercise training can likely be attributed to a number of factors that will be discussed below. These include factors related to the

subjects enrolled in each study in terms of age, gender, degree and duration of obesity, degree of visceral adiposity and baseline LV structure and function. the technique used in the assessment of LV structure and function can also explain this variability including its sensitivity, accuracy and degree of load-dependence. Finally, the exercise training intervention employed, its intensity, session duration, number of sessions per week and total duration of intervention, training intensity and mode of training ie. continuous versus interval.

2.4.3.1 Subject characteristics

Subjects enrolled in the studies discussed above included a wide range of age groups. This included children (Humphries et al., 2002), adolescents (Mitchell et al., 2002, Ingul et al., 2010), young to middle aged adults (Vogelsang et al., 2008, Baynard et al., 2008, Schuster et al., 2011, Millen et al., 2014) and older adults (Stewart et al., 2005, Eriksson et al., 2010). These differences make comparison between studies difficult. De Simone et al. (1995) showed that the variability of LVM in relation to height increases during human growth and that the allometric power exponent of LVM versus height in adults and children is lower that that derived for the entire age spectrum (de Simone et al., 1995). Hence, LVM/height$^{2.7}$, which is the most widely used scaling method in cardiac research, may not be appropriate when comparing studies involving different age groups. Furthermore, studies have used different scaling methods to normalise for body size differences, which would be expected to make comparisons between studies difficult.

2.4.3.2 Degree, duration and pattern of obesity

The discrepancy in the effects of training on LV structure and function in the literature could also be explained by the different degrees of obesity in the subjects enrolled. While most studies included obese subjects with BMIs between 30 and 35 kg.m^{-2}, some included overweight subjects with BMIs < 30 kg.m^{-2} (Millen et al. 2004, Eriksson et al. 2010) and others included subjects with BMIs > 35 kg.m^{-2}(Stewart et al. 2005 and Millen et al. 2014). No information was given in most of these studies on the duration of obesity in the subjects enrolled which might possibly have an influence on the effect of training. Indeed, Licata et al. (1992) showed that overweight individuals that had been overweight for less than 10 years had a significant increase in EF during exercise compared to those that had been overweight for more than 10 years, and a negative correlation was reported between the duration of obesity and the exercise-induced increase in EF (Licata et al., 1992).

More importantly, obesity is generally defined using BMI which incorporate both adipose tissue and muscle tissue and hence it does not account for individual differences in body composition and fat distribution. Individual differences in fat content and distribution is likely a relevant factor in the comparison between obese subjects. Some of the above mentioned studies measured fat content, and included subjects with ~30% fat (Humphries et al., 2002, Schuster et al., 2011) while others had ~ 38% fat (Stewart et al., 2005, Baynard et al., 2008) and ~ 44% fat (Mitchell et al,. 2002). Furthermore, the differences in fat distribution and the degree of visceral adiposity likely explain at least partly the disparity in the results. Schuster et al. (2011) showed that the greatest degree of improvement in LV structure and function following exercise was seen in the subjects with the greatest degree of visceral adiposity at baseline (Schuster et al., 2011). Two studies accurately measured visceral adipose tissue using MRI, one of which reported ~146 cm^3 (Stewart et al., 2005) while the other two were more than double this value; ~300 cm^3 (Mitchell et al., 2002) and ~350 cm^3 (Humphries et al., 2002). Other studies used waist circumference as a surrogate marker of visceral adiposity and were roughly within the same range. Additionally, some of these studies reported a significant reduction in %fat and/or visceral fat post-training (Humphries et al., 2002, Mitchell et al., 2002, Stewart et al., 2005, Ingul et al., 2010, Eriksson et al. 2010., Schuster et al., 2011, Sijie et al., 2012) and the majority of these studies reported some training effect on LV structure and/or function. Some authors attributed the lack of training effect on LV structure and function to insufficient loss of adipose tissue (Mitchell et al. 2002., Stewart et al., 2005 and Baynard et al., 2008). Additionally, Stewart et al. (2005) found a negative correlation between abdominal fat change and LVM change over time. This argument can be challenged by the fact that Eriksson et al. (2010) failed to detect any change in LVM after training either, though a significant reduction in WC and total body fat content were reported. Hence, other factors must be involved such as training intensity and duration.

2.4.3.3 Training intensity and duration

It is generally well-established that training type, intensity, duration and frequency are important determinants of the training-induced benefits of exercise (Shephard, 1968). In particular, heavy-intensity training was shown to induce superior cardiac benefits to moderate-intensity training (Wisloff et al., 2007) where heavy-intensity interval training induced LV structural and functional adaptations not achieved by moderate intensity training (Wisloff et

al., 2007). Heavy intensity training was shown to reduce cardiovascular mortality (Wisloff et al., 2006). Studies that have explored the impact of aerobic training on cardiac structure and function have used a variety of training durations and intensities ranging from short heavy-intensity programmes such as 10 days (Baynard et al., 2008) and 6 weeks (Millen et al. 2014), both of which did not result in any training-induced change in LV structure and function, to longer moderate or low intensity programmes including 6 months (Stewart et al., 2005) and 8 months (Eriksson et al., 2010). The majority of studies that have reported improvements in LV structure and/or function have used heavy-intensity programmes (Mitchell et al., 2002, Vogelsang et al., 2008, Sijie et al. 2012, Ingul et al., 2010.) for durations as short as 8 weeks to as long as 6 months.

2.4.4 Cardiac benefits of heavy-intensity interval training

Interval training generally consists of brief repetitive bouts of exercise at high intensities (~95% VO_{2max}) followed by periods of exercise at lower intensities. Interval training has the advantage of having rest periods that enable subjects to complete short bouts at higher intensity, which challenges the pumping ability of the heart (Wisloff et al., 2007). Furthermore, despite being an aerobic type of exercise, it includes periodic excursions into “anaerobic” energy pathways resulting in greater improvements in cellular signalling pathways involved in energy metabolism including mitochondrial biogenesis and the up-regulation of enzymes involved in glycolysis (Earnest, 2008). Wisloff et al. (2007) demonstrated that 12 weeks of heavy-intensity exercise training induced reverse LV remodelling and improvement in systolic function in cardiac patients, outcomes that were not achieved by moderate intensity continuous training (Wisloff et al., 2007). Furthermore, it was shown that heavy-intensity interval training attenuates post-myocardial infarction myocardial hypertrophy, increases cardiac myocyte contractile function and increases SERCA-2 expression and Ca^{2+}-sensitivity of the myofilaments (Wisloff et al., 2002). Additionally, high-intensity interval training was shown to significantly increase insulin-sensitivity (Hood et al., 2011) and improves skeletal muscle mitochondrial capacity (Little et al., 2010). In the context of obesity, heavy-intensity interval training was shown to improve LV systolic and diastolic function, however studies exploring the impact of heavy-intensity interval training on cardiac structure and function in healthy obese individuals are limited. Ingul et al. (2010) showed that 13 weeks of high-intensity interval training restored an impaired LV systolic and diastolic function in obese

healthy adolescents (Ingul et al., 2010). Sijie et al. (2012) showed that 12 weeks of both heavy-intensity interval training and moderate intensity continuous training resulted in significant improvement in LV systolic function, though greater with interval training, and significant reduction in %fat and waist to hip ratio in overweight adults (Sijie et al., 2012). To date, evidence suggest that the superior benefits provided by interval training result from the higher intensities used in this type of training. It is not known, however, if the repetitive pattern of exercise has any additional impact on cardiac structure and function in obesity. Studies comparing the impact of work and intensity-matched continuous and heavy intensity exercise training on LV structure and function in healthy obese individuals have not been carried out.

2.5 Summary and thesis aims

Overweight and obese women are particularly at risk of heart disease. Obesity induces unfavourable alterations in LV structure, morphology and function that increase in severity with increasing degrees of obesity, in particular, abdominal adiposity. It is not clear, however whether obesity induces concentric or eccentric LV remodelling. Extensive evidence exists suggesting that body size and composition are physiologically related to LV size and morphology in a non-linear fashion, calling for a need to normalise cardiac structural variables for individual differences in body size and composition using allometric scaling procedures. The physiological impact of body size and composition on LV functional variables, notably novel echocardiographic measures of LV systolic and diastolic function including myocardial velocity, deformation and torsion, and whether there is a need to normalise these variables for body size and/or composition has not been previously investigated in healthy obese women.

Exercise training improves LV structure and function in obese individuals. It was shown that aerobic exercise training induces LV reverse remodelling and restores normal LV systolic and diastolic function in obese individuals without the need to restrict caloric intake or reduce weight. The optimum exercise type for improving LV structure and systolic and diastolic function, notably myocardial velocity, deformation and torsion has not yet been established. The benefits of aerobic training on cardiac structure and function appear to be higher with higher training intensities. Little is known about the LV systolic and diastolic functional responses to heavy-intensity exercise, in particular LV myocardial velocity, deformation and torsion.

Heavy-intensity interval training has recently been suggested as a more beneficial life style intervention to improve cardiac function in obese individuals. However, the impact of interval training on LV structure and function has not been compared with continuous training in overweight/obese women. Additionally, it is not known, whether the repetitive pattern of interval training provides any additional benefit on LV structural and functional exercise-induced alterations, particularly in obese women.

Therefore, the aims of this thesis are:

1. To assess the impact of excess adipose tissue, particularly visceral adipose tissue, on LV size, morphology and function in overweight and obese women after normalising for body size and composition using study specific allometric power exponents.
2. To establish which body size variable/composition variable best accounts for individual differences in body size by allometric scaling without masking the influence of excess adipose tissue
3. To compare the LV systolic and diastolic functional response to heavy-intensity exercise in healthy obese and non-obese women using novel echocardiographic techniques
4. To compare the effects of work- and intensity-matched interval and continuous exercise training on LV structure and function in overweight and obese women.

Chapter 3 General Methods

3.1 Participant recruitment and screening

Participants were recruited via local poster advertisements and e-mail advertisements to participants who had previously given consent to be contacted for future studies. Ethical approval for all studies was granted by the University of Leeds Faculty of Biological Sciences Ethics committee which followed the principles outlined in the Declaration of Helsinki. Studies in chapters 4 and 6 were granted ethics approval through the same ethics application and the study in chapter 5 was granted ethics approval through a separate ethics application (see Appendix 1). Participant information sheets were provided and full informed consent was obtained prior to all data collection (see Appendix 2). Participants were verbally informed of all procedures to be undertaken and, where appropriate, familiarisation with measurements and techniques was provided. At initial contact with participants, inclusion criteria were confirmed verbally. Individuals were excluded from the studies if they were smokers, utilising any form of prescribed medication, had known cardiovascular, pulmonary and metabolic disease, musculoskeletal impairment, cancer, contraindication to exercise or clinical, electrocardiographic or echocardiographic evidence of structural heart disease not directly related to obesity. Participants were given at least 24 hours to read through the information sheets and to ask any questions. Finally, participants were requested to sign written consent and complete a physical activity readiness questionnaire which was used to further identify any exclusion criteria.

3.2 Experimental protocols

Each study's experimental procedures are detailed in the individual chapters. All visits took place in temperature controlled exercise physiology laboratories at the University of Leeds. For the echocardiographic assessment and the assessment of cardio-respiratory fitness, participants were instructed to refrain from performing exercise activity and drinking alcohol and caffeine in the 12 hours prior to the test. For the measurement of body composition, participants were instructed to arrive at the laboratory following an overnight fast of at least 12 hours.

3.3 Assessment of body size and composition

3.3.1 Body mass index (BMI) and body surface area (BSA)

Participants' height (HT) and body mass (BM) were measured using a stadiometer and manual calibrated scales to the nearest 0.5 cm and 0.1 kg respectively. BMI was determined using the following equation:

$$BMI\ (kg/m^2) = BM\ (kg)/\ Ht^2\ (m)$$

Body surface area (BSA) was calculated from the following equation developed by Dubois and Dubois (1916):

$$BSA\ (m^2) = BM^{0.425} \times HT^{0.725}$$

3.3.2 Waist-hip ratio (WHR)

Waist circumference was measured, as an index of visceral adiposity, by placing a tape measure around the abdomen at a position midway between the uppermost border of the iliac crest and the lower border of the costal margin. Hip circumference was measured as the widest part of the hip region. Both waist and hip circumferences were measured to the nearest 0.5 cm. Waist to hip ratio was determined using the following equation:

$$WHR = WC\ (cm)/\ HC\ (cm)$$

Where WC = waist circumference and HC = hip circumference

3.3.3 Bioelectrical impedance analysis (BIA)

Measurement of body fat, including fat mass (FM), fat-free mass (FFM) and fat percent (FP) was performed using a commercially available bioelectrical impedance analyser (Bodystat 1500, Isle of Man, UK). BIA is a safe, rapid, inexpensive and non-invasive technique to estimate body fat content, and requires minimal operator training.

3.3.3.a Principle of BIA

Bioelectrical impedance analysis (BIA) measures the impedance or resistance to the flow of an electric current through the body fluids. Impedance is low in fat-free tissue where intracellular and extracelllular fluid (ICF and ECF respectively) and electrolytes are primarily situated, whereas in fat tissue have a high impedance. Impedance is the product of resistance and reactance. Resistance is the resistance to current flow through the body, whereas reactance is the frequency-dependent resistance to current flow that happens in cell membranes, that separate the extracellular from

the intracellular fluid compartments, being poor electric conductors, due to their capacitating nature (Buchholz et al., 2004, Kushner, 1992). At a fixed frequency of 50 kHz, a small constant current passed between electrodes spanning the body flows through both the ECF and ICF (Kushner, 1992). The voltage drop between electrodes provides a measure of impedance that is subsequently converted to a corresponding estimate of TBW via prediction equations. Prediction equations used by Bodystat 1500 have been generated in populations of obese females, comparable to most participants in these studies. FFM is then calculated from this estimate using an assumed hydration fraction for lean tissue. FM and PF are then calculated as follows:

$$FM\ (kg) = BM\ (kg) – FFM\ (kg)$$

$$FP\ (\%) = FM\ (kg) / BM\ (kg) \times 100$$

Where FM = fat mass, BM = body mass, FFM = fat-free mass

3.3.3.b BIA experimental procedure

Subjects were instructed to attend for BIA measurements following an overnight fast of at least 12 hours and to void their bladder 30 min prior to the measurement. After 10 minutes of rest in the supine position, four self-adhesive, disposable electrodes were connected to the subject's left side, two at the wrist and two at the ankle, immediately after wiping the skin with alcohol in order to remove skin resistance. The subject's age, sex, weight and height were entered manually into the analyser before a small constant current of 400 uA at a fixed frequency of 50 kHz was passed between electrodes. FFM, FM and FP are then displayed on the BIA analyser screen.

$$FM\ (kg) = BM\ (kg) – FFM\ (kg)$$

$$FP\ (\%) = FM\ (kg) / BM\ (kg) \times 100$$

Where FM = fat mass, BM = body mass, FFM = fat-free mass

3.3.3.c Validity and reliability of BIA

The validity and reliability of this method has been confirmed by previous studies (Lukaski et al., 1985, Buchholz et al., 2004)

3.4 Echocardiographic assessment of LV structure and function

Left ventricular structure and function were assessed using echocardiography, which is a non-invasive imaging technique that utilises ultrasound waves to provide images of the heart. Several approaches can be adopted using echocardiography depending on the site from which the heart is visualised. Transthoracic echocardiographic, which is the approach used used for this work, is the standard approach and consists of acquiring ultrasonic images of the heart from the anterior aspect of the subject's chest wall. Several echocardiographic modalities have been employed in this work for the quantitative assessment of LV structure and function. These include standard two-dimensional (2D) imaging, motion-mode (M-mode), pulse wave Doppler (PWD), tissue Doppler imaging (TDI) and two-dimensional speckle tracking (2DST).

Echocardiographic image acquisition was carried out using a commercially available ultrasound system (Vivid 7, GE Medical Systems, Horten, Norway) and a 1.6 - 4 MHz phased array transducer with the subject lying in the left lateral decubitus position. Subjects were instructed to breath hold during image recording and at least three cardiac cycles were stored digitally in raw DICOM format to CD/DVD or USB archive. Off-line analysis was carried out using commercially available software (Echo-pac, GE Medical Systems, Horten, Norway, version 7.0.0) and the average of at least 3 consecutive cardiac cycles was taken for all measurements.

3.4.1 Standard 2D and M-mode Echocardiography

Two-dimensional images were acquired in accordance with the American Society of Echocardiography (ASE) (Henry et al., 1980). Harmonic imaging was used and images were optimised to maximise spatial and temporal resolution by adjusting gain, dynamic range, depth, angle width, frame rate and frequency.

Initially, a 2D parasternal long-axis (PLAX) view was obtained (Figure 3.1). An M-mode axis passing beyond the tip of the mitral valve at mid-chordal level, perpendicular to the LV long axis was acquired for the measurement of the diastolic and systolic interventricular septum thickness (IVSTd and IVSTs), LV posterior wall thickness (PWTd and PWTs) and LV internal diameter (LVIDd and LVIDs) performed from leading edge to leading edge. Systolic measurements were taken at end systole identified as the point of narrowest LV internal dimension whereas diastolic measurements were

taken at end diastole identified as the point of widest diameter (Sahn et al., 1978). The subsequent calculation of LV mass (LVM) was carried out using the equation developed and validated by Devereux (Devereux et al., 1986) showing a significant correlation (r = 0.92) with post-mortem findings:

$$LVM\ (g) = 0.8 \times (1.04\ [(LVIDd + PWTd + IVSTd)^3 - (LVIDd)^3] + 0.6\ g$$

The relative wall thickness (RWT), an index of LV concentric morphology (Grossman et al., 1977) was also calculated as follows:

$$RWT = (IVSTd + PWTd) / LVIDd$$

Fractional shortening (FS), a 2D measure of systolic contractile function was calculated as follows:

$$FS\ (\%) = (LVIDd - LVIDs) / LVIDd \times 10^{-2}$$

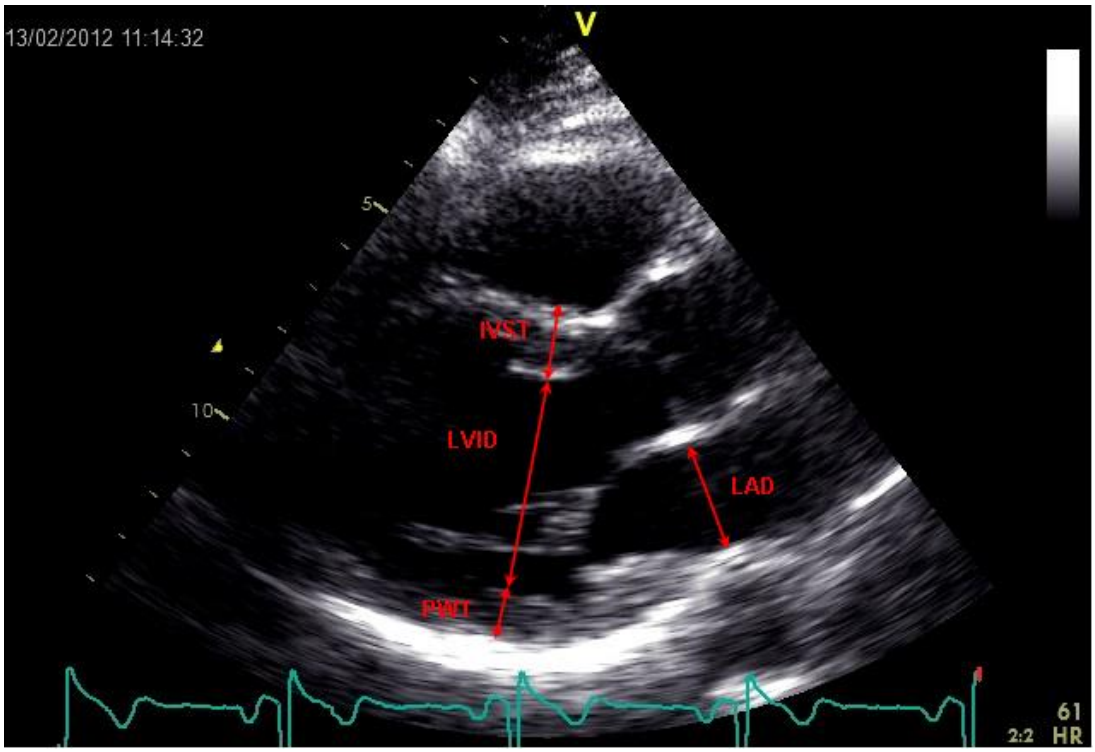

Figure 3. 1 LV Standard Parasternal Long Axis view. IVST: interventricular septal thickness, LVID: left ventricular internal diameter, PWT: posterior wall thickness, LAD: left atrial diameter

In the same view, an M-mode axis through the left atrium across the aortic annulus was carried out for the measurement of its anterior-posterior diameter (LAD) in end systole.

Epicardial fat thickness was measured as proposed by (Iacobellis and Willens, 2009) as the echo-free space between the outer wall of the right ventricular myocardium and the visceral pericardium in three different cardiac cycles at end-systole (Figure 3.2). The average of three measurements at both parasternal long-axis (PLAX) and short-axis (PSAX) views was calculated. For the PLAX view, maximum EFT was measured along the midline of the ultrasound beam, perpendicular to the aortic annulus, used as an anatomical landmark. Whereas, for the PSSX view, maximum EFT was measured along the midline of the ultrasound beam, perpendicular to the interventricular septum at mid-chordal and tip of papillary muscles levels. We have recorded intra and interobserver intraclass correlation coefficients of x and y, respectively for this assessment.

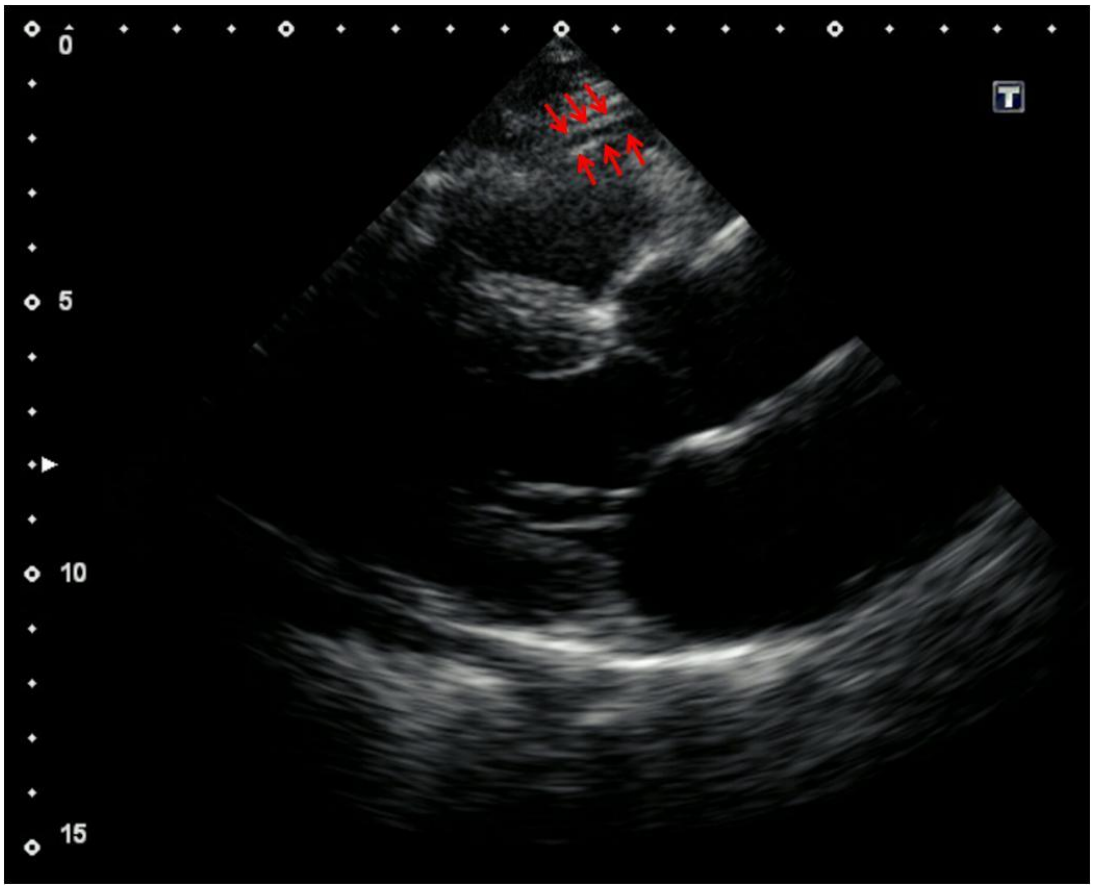

Figure 3. 2 Epicardial fat thickness measurement. In the parasternal long axis view, epicardial fat thickness (between red arrows) is identified as the echo-free space between the outer wall of the right ventricular myocardium and the visceral pericardium

Left ventricular and atrial volumes were measured using the Simpson's biplane method as recommended by the ASE (Lang et al., 2005) which consists of manual endocardial border tracing at end-diastole, defined as

the frame immediately following mitral valve closure, and end-systole, defined as the frame immediately prior mitral valve opening, in two tomographic planes; transthoracic apical four-chamber (A4C) and two-chamber planes (A2C). The area is subsequently divided into a series of stacked discs and the LV and LA volumes are calculated as the sum of all the disks using the following equation:

$$\text{Volume} = \pi / 4 \, (h) \, \Sigma \, (D1) \, (D2)$$

where h is the height of each disk and D1 and D2 are the orthogonal minor and major axis of each disk. Left ventricular ejection fraction (EF) a commonly used measure of global LV function was calculated as follows (Pombo et al., 1971):

$$EF \, (\%) = (EDV - ESV) / EDV \times 10^{-2}$$

3.4.2 Standard Pulse Wave Doppler (PWD) echocardiography

Standard PWD echocardiography assesses the global LV diastolic function by measuring the velocity of flow through the mitral valve in the A4C view in accordance with the Canadian Consensus Recommendations (Rakowski et al., 1996). A 4mm sample volume was placed at the tips of the mitral valve parallel to mitral inflow giving rise to a spectral signal reflecting diastolic mitral inflow for the measurement of peak flow velocities in early (E) and late diastole following atrial contraction (A) and the early diastolic flow deceleration time (DCT; Figure 3.3). The E/A ratio was also calculated. Isovolumic relaxation time (IVRT) was measured at the apical 3 chamber (A3C) view by placing a 4 mm sample volume in both the LV inflow and outflow and was defined as the time interval from between aortic valve closure and mitral valve opening.

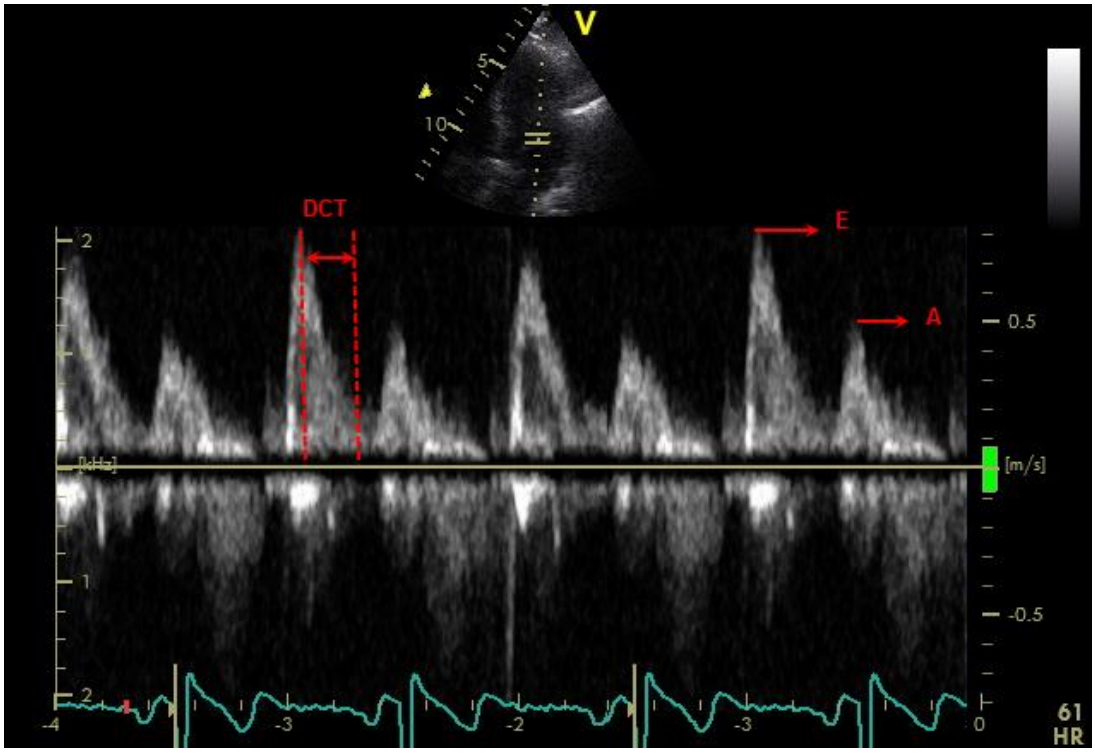

Figure 3. 3 Mitral Inflow Pulse Wave Doppler (PWD) echocardiography. DCT = deceleration time, E = peak early diastolic inflow velocity, A = peak late (atrial phase) diastolic inflow velocity.

3.4.3 Tissue Doppler Imaging (TDI) echocardiography

Whilst in the A4C view, the TDI mode was activated and a 2 mm sample volume was placed on the septal and lateral aspects of the mitral annulus. In the subsequent spectral trace, peak myocardial velocities were measured, including systolic myocardial velocity (Sm), early diastolic myocardial velocity (Em) and late diastolic myocardial velocity following atrial contraction (Am; Figure 3.4). An average of the septal and lateral mitral annular velocities was calculated, from which E/Em was derived. E/Em is a validated surrogate index for LV end-diastolic filling pressure (Ommen et al., 2000). Additionally, myocardial performance index (MPI), an index of combined global systolic and diastolic performance, was calculated as follows: [(a – b) / b] where (a) is the time interval from the end to the onset of diastolic myocardial velocity and (b) is the ejection time (Tei et al., 1995) (Figure 3.5).

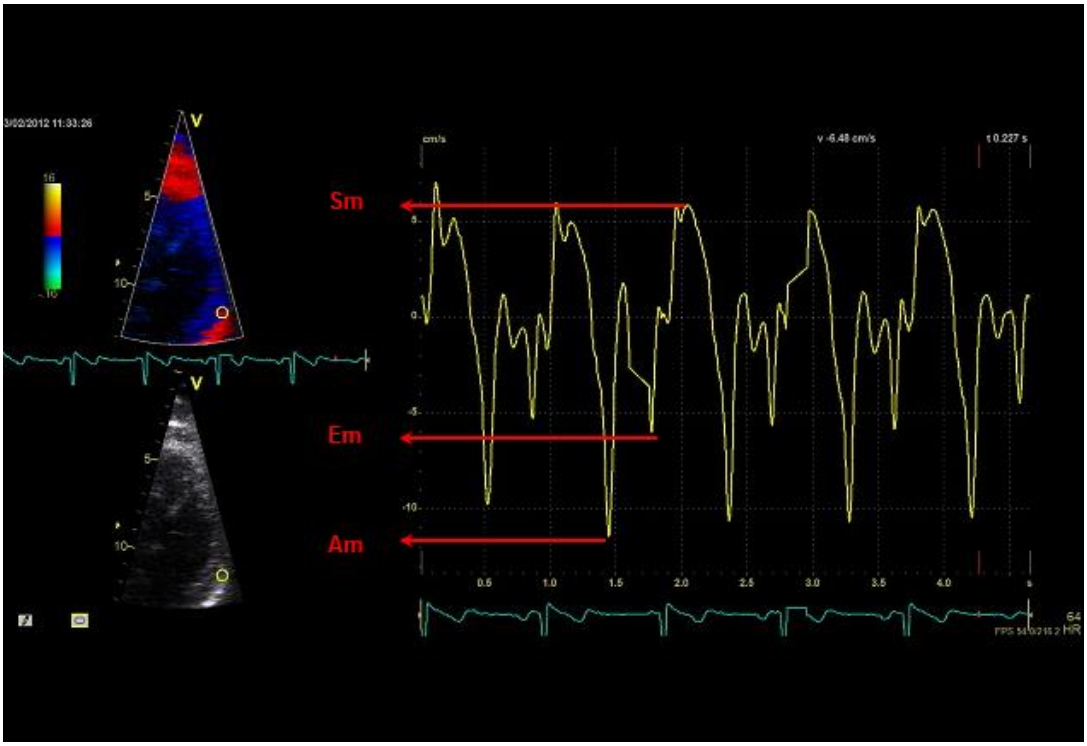

Figure 3. 4 Tissue Doppler Imaging echocardiography at the lateral annulus. Sm = peak systolic myocardial velocity, Em, peak early diastolic myocardial velocity, Am = peak late (atrial phase) diastolic myocardial velocity.

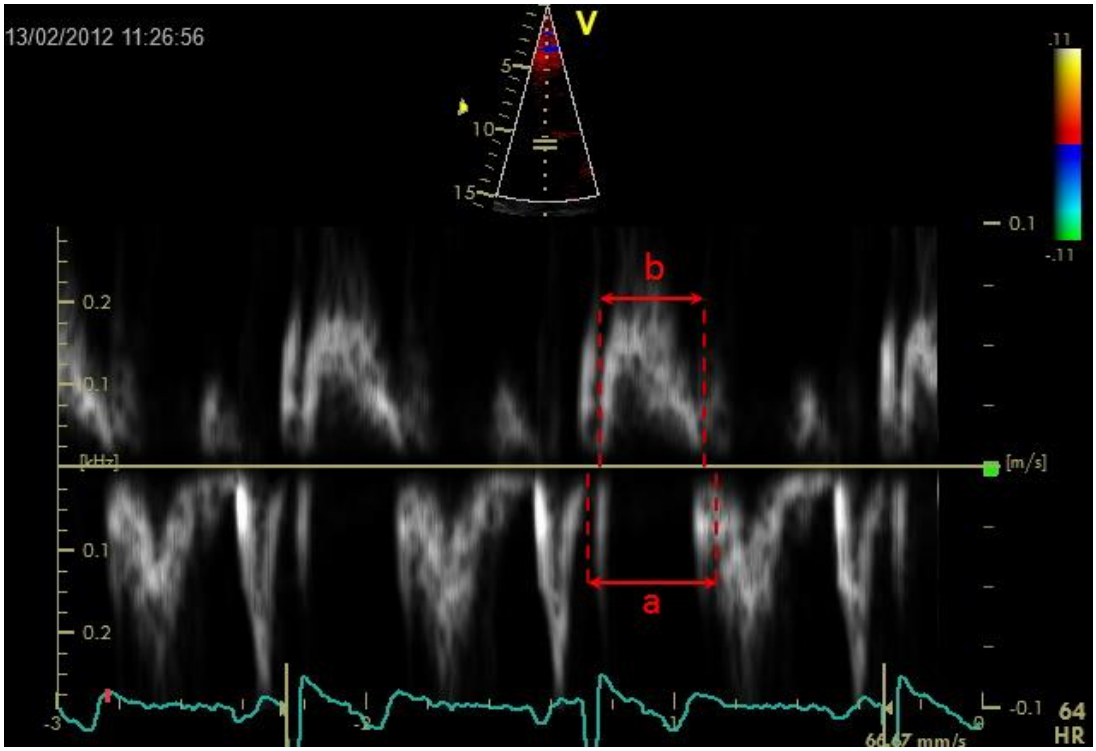

Figure 3. 5 TDI- derived Measurement of Myocardial Performance Index (MPI). a = time interval from end to onset of diastole, b = ejection time.

3.4.4 Two-Dimensional Speckle Tracking (2DST) echocardiography

Two-dimensional speckle tracking (2DST) echocardiography was carried out to assess LV strain (S) and strain rate (SR) in the longitudinal, circumferential and radial directions. The assessment of longitudinal strain (LongS) and strain rate during systole (LongSRs) and early and late diastole (LongSRe and LongSRa respectively) was carried out on standard 2D images taken from the A4C and A2C views (Figure 3.6 and 3.7).

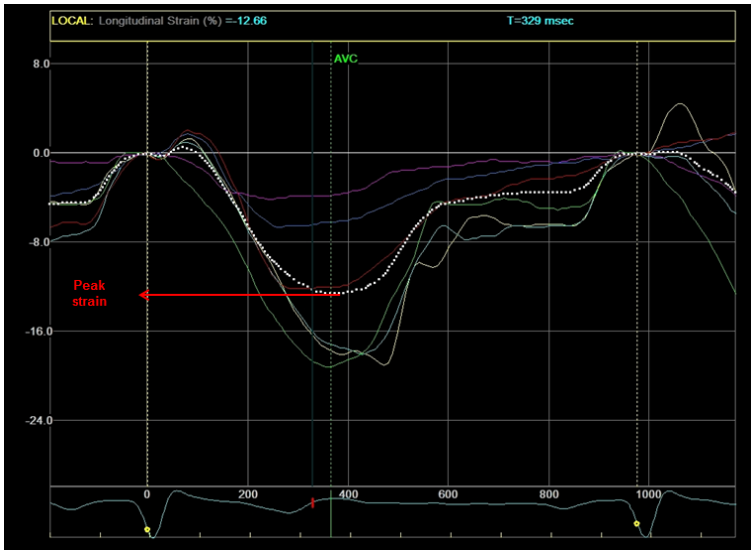

Figure 3. 6 Longitudinal strain curves from the apical 4-chamber view

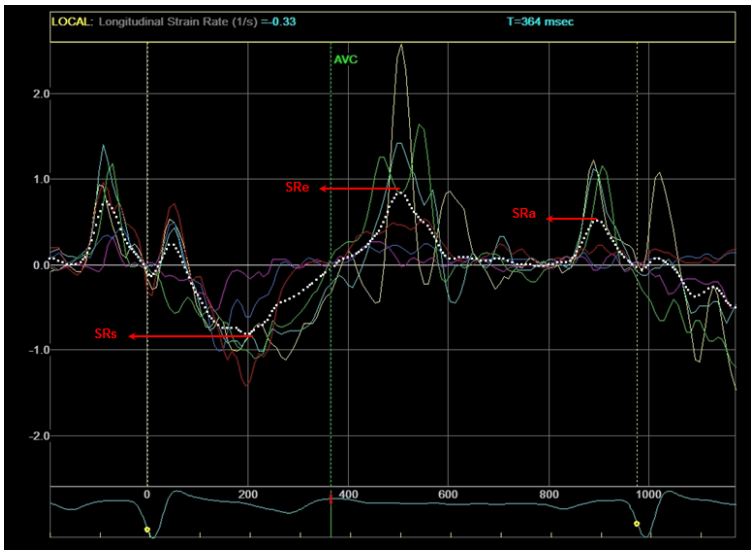

Figure 3. 7 Longitudinal SR curves from the apical 4-chamber view. SRs = systolic SR, SRe = early diastolic SR, SRa = late diastolic SR.

The assessment of LV circumferencial and radial strain (CircS and RadS respectively) and strain rate during systole (CircSRs and RadSRs respectively), early diastole (CircSRe and RadSRe respectively) and late diastole (CircSRa and RadSRa respectively) was carried out on standard 2D images from the PSAX view at the basal level of the LV. This was achieved by placing the ultrasound beam at the level of the tips of the mitral valve leaflets (Park et al., 2008). These images were also used for the assessment of basal rotation. As for the assessment of apical rotation and subsequently LV torsion (LVTor), an additional standard 2D image was taken at the PSAX view at apical level of the LV by placing the ultrasound beam just proximal to the level of obliteration of LV lumen (van Dalen et al., 2008). Torsion was calculated as the difference between basal and apical rotations at the same time point. All images were taken at end expiration. In the apical views, the focal point was positioned at the mitral valve whereas in the PSAX views the focal point was positioned at the centre of the LV to minimise the effects of beam divergence. The sector width and depth were adjusted to allow frame rates between 40 and 90 frames per second (Artis et al., 2008). Off-line analysis of S, SR, rotation and LVTor was carried out by allocating a region of interest (ROI) in all views by tracing of the endocardial border of the entire LV followed by the adjustment of endocardial and epicardial alignment and continuous frame-by-frame tracking of “natural acoustic markers” (Figure 3.8 and 3.9) (Korinek et al., 2005). Subsequent S and SR were calculated from the amount and rate of displacement of the acoustic markers. The analysis software automatically graded the tracking quality of each segment of the LV as either acceptable or unacceptable, in which case they were excluded (Figure 3.10 and 3.11). The average of the tracked segments of each wall of the LV in each view were used in the analysis.

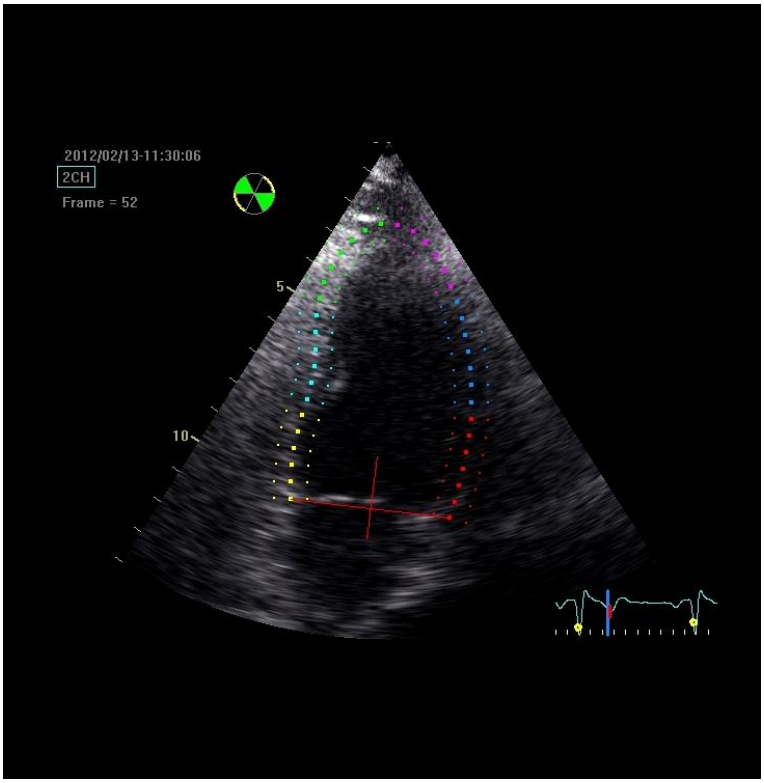

Figure 3. 8 Region of interest for 2DST in the apical 4-chamber view.

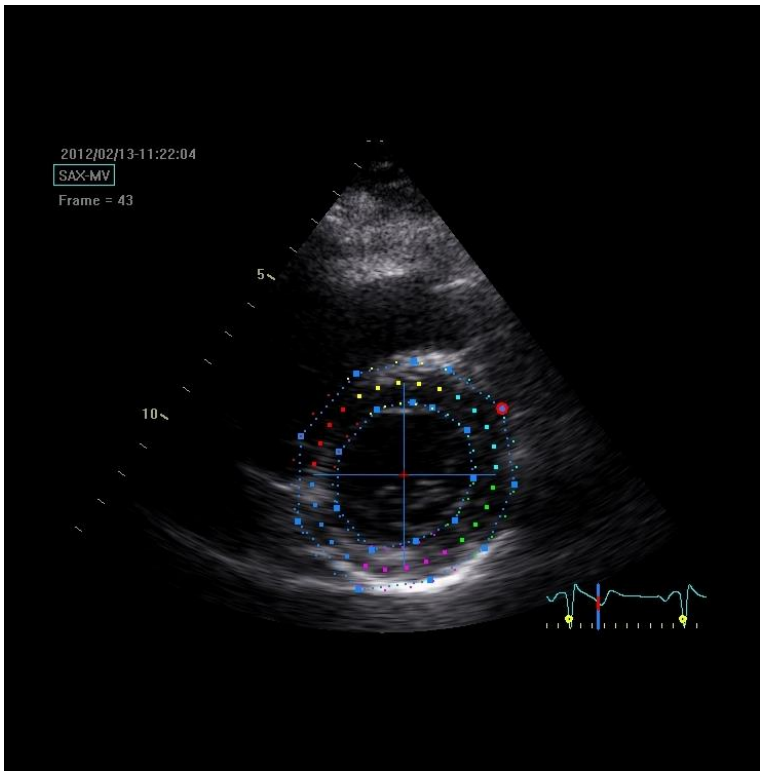

Figure 3. 9 Region of interest for 2DST in basal parasternal short axis view.

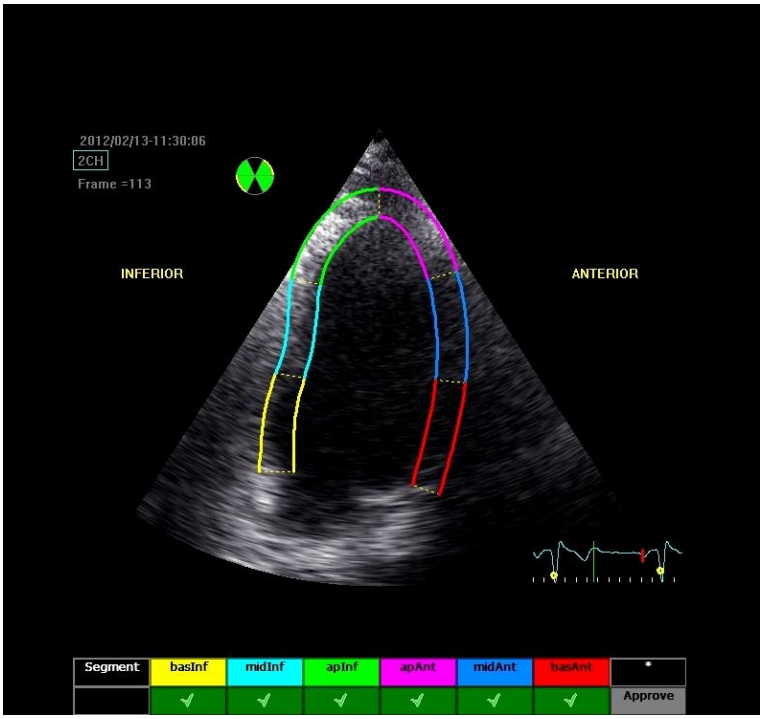

Figure 3. 10 Automatic software grading of tracking quality for 2DST in apical 2-chamber view

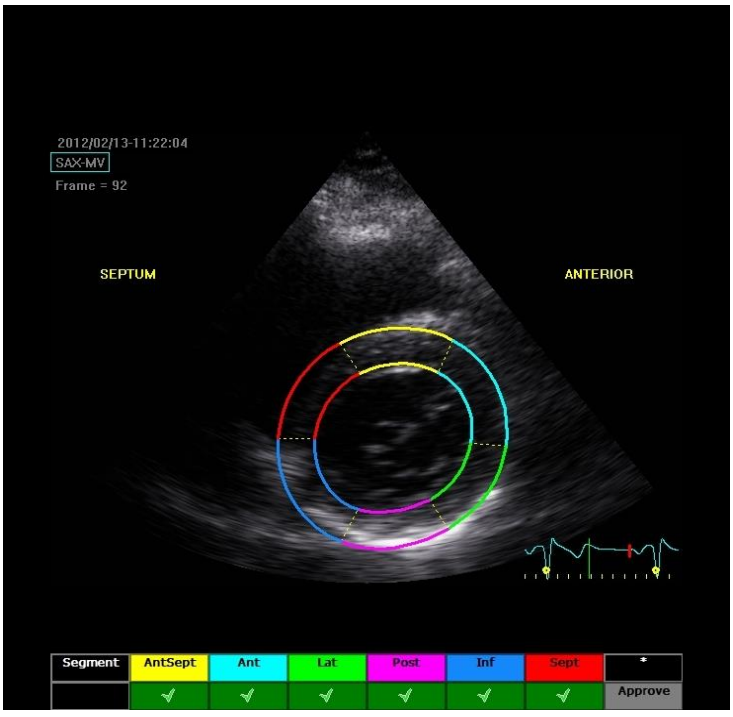

Figure 3. 11 Automatic software grading of tracking quality for 2DST in parasternal basal short-axis view

The intra-observer variability for echocardiographic measurements was minimal with co-efficients of variation ranging between 4% and 13%. Table 3.1 shows the coefficients of variation for the echocardiographic measured variables.

Variable	Coefficient of variation
EFT	4.9 %
IVSTd	4 %
LVIDd	4.6 %
LVPWd	4.4 %
E	10,4 %
A	9.3 %
DCT	6.8 %
IVRT	9.7 %
EDV	9.4 %
ESV	10 %
Sm	6.4 %
Em	6.2 %
LongS	5.7 %
LongSRs	8.3 %
LongSRe	7.9 %
LongSRa	8.4 %
CircS	8 %
CircSRs	10.8 %
CircSRe	11.6 %
CircSRa	12.3 %
RadS	9.3 %
RadSRs	11.4 %
RadSRe	12 %
RadSRa	11.8 %
Torsion	12.7 %

Table 3. 1 Intra-observer variability for echocardiographic measurements

3.5 Assessment of cardio-respiratory fitness (CRF)

Cardiorespiratory fitness was assessed by measuring the maximal aerobic capacity (VO_{2max}) and lactate threshold (LT) recorded during cardio-pulmonary exercise (CPX) tests. These variables were also used to determine the desired work-rate (WR) during subsequent exercise sessions. Furthermore, LT was used as a reference point between moderate and heavy-intensity domains (Rossiter, 2011).

3.5.1 Cardio-pulmonary exercise (CPX) test

In order to determine maximal oxygen uptake (VO_{2max}) and LT, a CPX test was performed by participants. This consisted of a ramp incremental (RI) exercise test followed by a step exercise (SE) stage (Figure 3.12). For chapter 5, the CPX test was performed in the seated position on an electronically braked bicycle ergometer (Excalibur Sport V2.0; Lode BV, Groningen, The Netherlands) whereas for chapter 6 it was performed in the semi supine position on an echocardiography-compatible supine bicycle ergometer (Lode BV Medical Technology, Groningen, Netherlands). In all tests, a nose clip and a mouth piece were fitted. Breath by breath analysis of expired gas was undertaken using oxygen and carbon dioxide analysers (Breeze Suite software V.5.0 and V.7.2, Medgraphics D-series; Medgraphics, Medical Graphics Corporation, St Paul, MN, USA).

The RI test consisted of an initial 4 min rest period, followed by 4 min of cycling at 20 W until gas exchange reached a steady state, defined by a respiratory exchange ratio (RER) between 0.75 - 0.9. At this point, the RI test began at a rate of 12 W/min during which participants were instructed to maintain a cadence of > 60 rpm and encouraged to carry on until volitional fatigue. The test was terminated when participants could no longer maintain a cadence of ≥ 50 rpm despite strong encouragement. Throughout the test, heart rate (HR) and blood pressure (BP) were measured every 2 minutes using a 12-lead ECG and a sphygmomanometer respectively. Additionally, the rate of perceived exertion (RPE) was measured every 2 minutes using the Borg's scale of 6 – 20.

At the end of the RI test, maximal WR was calculated as follows:

$$WR_{peak}\ (W) = \text{RI test duration} \times \text{ramp rate} + 20$$

Where 20 is the initial WR during the 4 min cycling prior to the initiation of the RI test.

After the RI test, a step exercise (SE) was carried out. The participants cycled for 5-min at 20 W and then WR was increased to 105% of WR_{peak} recorded in the RI test. Participants cycled at a high cadence (> 80 rpm) until volitional fatigue followed by a cool-down period of 5 min of cycling at 20 W. The SE stage was used to confirm whether VO_{2max} was achieved at the end of the RI test in case a plateau was not reached (Rossiter et al., 2006).

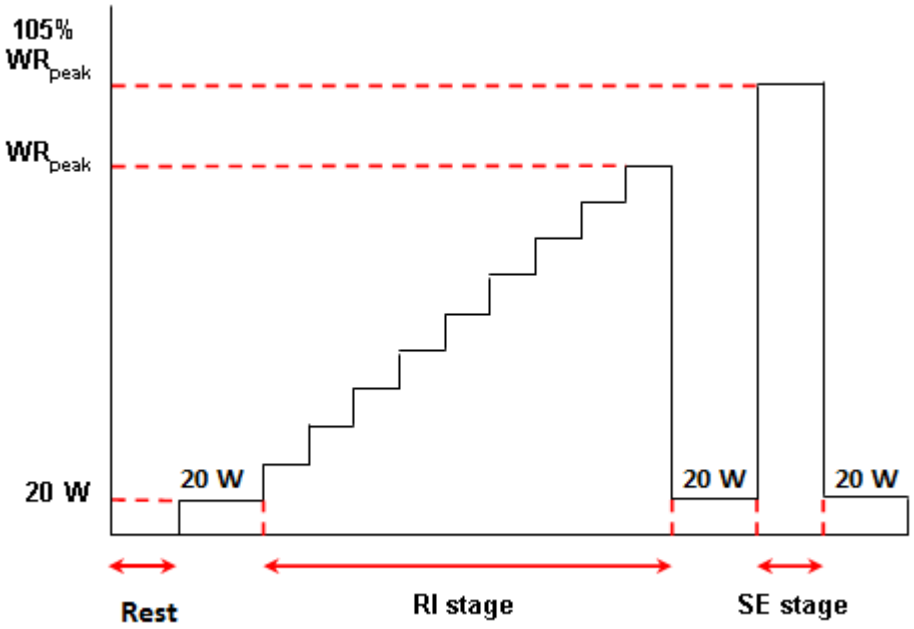

Figure 3. 12 Schematic representation of the cardio-pulmonary exercise test for the assessment of cardio-respiratory fitness. A rest period was followed by 5 min of cycling at 20 W before the ramp incremental (RI) stage was initiated. This was followed by 5 min of cycling at 20 W before the step exercise (SE) stage was initiated. Finally, the test ended with a 5 min cool-down period.

3.5.2 Calculation of VO_{2max} and lactate threshold (LT)

Exported breath by breath data was analysed using OriginLab software (OriginPro 8, OriginLab, Northampton, MA, USA). Peak oxygen uptake (VO_{2peak}) was calculated as the highest average value of 12 consecutive breaths from RI and SE parts of the CPX test (Bowen et al., 2012). For chapters 5 and 6, a paired t-test indicated that the VO_{2peak} values from the RI and SE stages of the test were not significantly different, therefore VO_{2max} was calculated as the average of the VO_{2peak} values from the RI and SE. The relative VO_{2max} was calculated by dividing the absolute VO_{2max} by BM (kg). Lactate threshold was estimated non-invasively using the V-slope method. This method consisted of identifying the point of inflection on the curve of VO_2 plotted against VCO_2 (Beaver et al., 1986). In order to confirm this point, further checks were performed to ensure a rise in end tidal O_2 and a plateau in end-tidal CO_2 coincided with this point (Whipp et al., 1986) (Figure 3.13). The estimation of LT was carried out by at least 2 researchers and the average was reported.

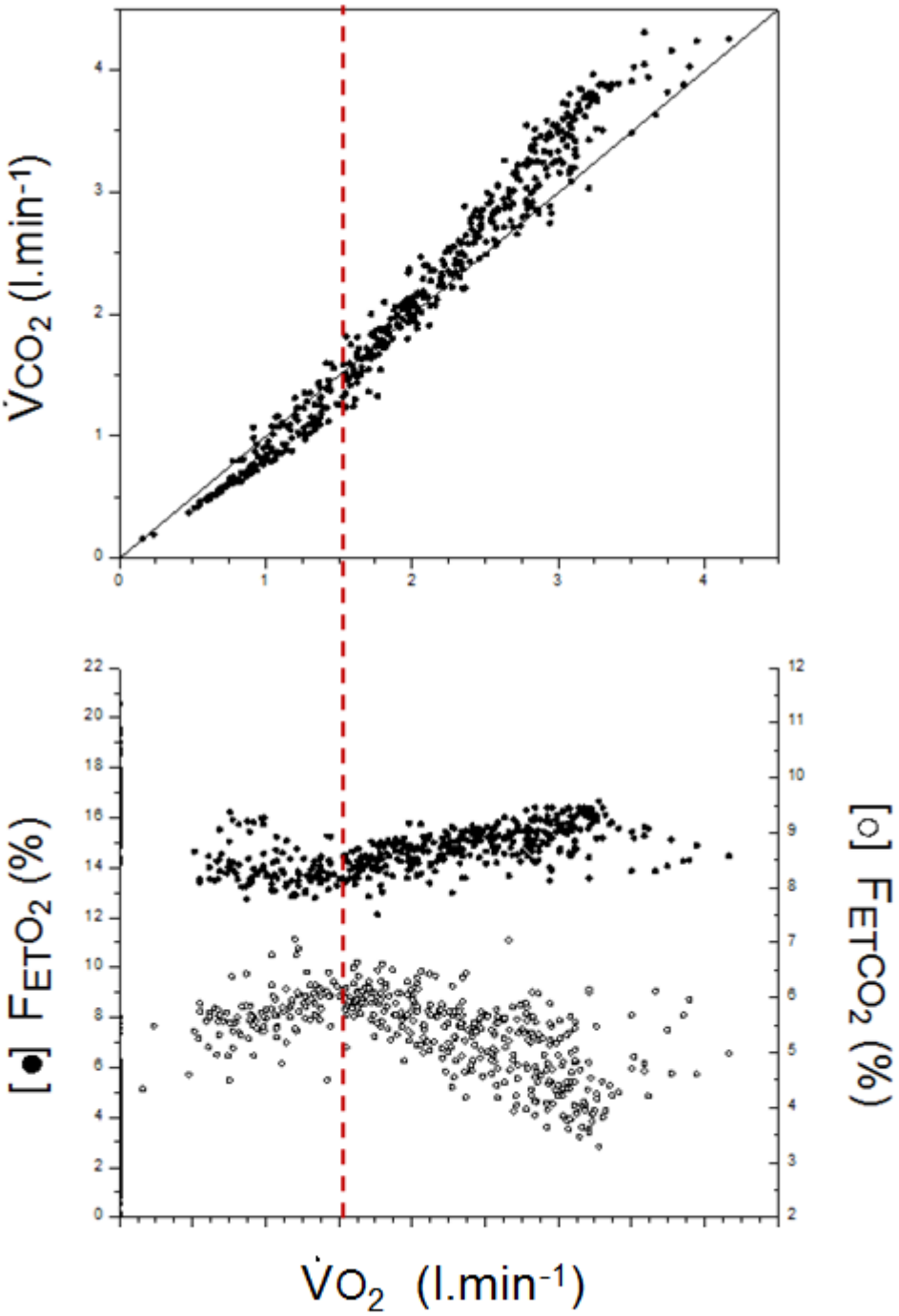

Figure 3. 13 Calculation of lactate threshold (LT; red shaded line) using the V-slope method. LT was confirmed by ensuring the identified point coincided with a rise in end-tidal O_2 and a plateau in end-tidal CO_2.

3.6 Statistical analysis

All statistical analyses were carried out using software (SPSS v.19, IBM Corporation, Somers, NY, USA). Initially, all data were examined for normal distribution using the Kolmogorov-Smirnov test. In the event where data were not normally distributed, non-parametric tests were carried out. In chapter 4, the allometric relationship between variables was assessed using the equation of the general form ($y = x^b$) as y = dependent variable, x = independent variable and *b* = the beta exponent of the slope of the log-linear plot. Pearson correlations were carried out to assess inter-variable relationships. In chapter 4, a one-way ANOVA was performed to compare between groups. In chapters 5 and 6, Student's independent t-tests were performed to compare between groups' resting values (chapter 5) and baseline values (chapter 6). The effects of exercise and recovery (chapter 4) and exercise training (chapter 5) were assessed using ANOVA with repeated measures. When baseline values were significantly different between groups, they were entered as covariates in the model. Cohen's d was calculated to assess effect size as the difference between rest and recovery means (chapter 5) or pre and post-training means (chapter 6) divided by the standard deviation of the variable (Field, 2013). Significance was accepted as $P < 0.05$.

Chapter 4 The relationship between left ventricular structure and function, and indices of obesity in overweight and obese women

Aspects of this chapter were presented at the following conferences:

- Annual Faculty of Biological Sciences Postgraduate Symposium, University of Leeds, UK, March 2011
- Europrevent 2012 - European Society of Cardiology, Dublin, May 2012
- The Systems Biology of Exercise: Cardio-respiratory and Metabolic Integration, University of Leeds, UK, August 2012

4.1 Introduction

Obesity is a global epidemic with a progressively increasing world-wide prevalence (Ogden et al., 2014, Rennie and Jebb, 2005, WHO, 2014). Women, have a higher risk of heart failure compared to men (Kenchaiah et al., 2002). Furthermore, obesity, and particularly abdominal adiposity, was shown to increase the risk of heart failure in women but not in men (Dagenais et al., 2005).

Obesity induces unfavourable LV structural and functional alterations in otherwise healthy obese individuals that remain silent for years before progressing to overt heart failure (Chinali et al., 2006, Di Salvo et al., 2006, Koopman et al., 2012, Pascual et al., 2003, Peterson et al., 2004, Tumuklu et al., 2007, Wierzbowska-Drabik et al., 2013, Wong et al., 2004). With regards to LV morphology, obesity has traditionally been associated with eccentric LV morphology (Koopman et al., 2012, Pascual et al., 2003). An increasing number of studies have recently challenged this notion by reporting LV concentric morphology in otherwise healthy normotensive obese individuals (Wong et al., 2004, Woodiwiss et al., 2008, Peterson et al., 2004). This appears to be related to increasing excessive visceral adipose tissue rather than a general increase in body fat (Neeland et al., 2013). As for LV function, depending on the echocardiographic technique used, results have been variable. Standard echocardiography tended to present a classic pattern of LV diastolic dysfunction with preserved systolic function (Wong et al., 2004, Peterson., 2004), or even sometimes

supernormal systolic function (Di Bello et al., 2006, Iacobellis et al., 2002). Novel techniques such as TDI and 2DST have shown subtle changes in both systolic and diastolic dysfunction (Barbosa et al., 2013, Shah and Solomon, 2012, Wierzbowska-Drabik et al., 2013, Wong et al., 2004). Furthermore, visceral fat, particularly epicardial fat, has recently been identified as the principal mediator of adverse LV structural and functional changes (Iacobellis and Willens, 2009). Indeed, echocardiographic epicardial fat thickness is suggested as a more accurate surrogate marker of visceral adiposity than waist circumference and is believed to have, in addition to endocrine and paracrine effects, local mechanical influence on cardiac function (Crendal et al., 2014).

In order to properly explore the impact of obesity on LV size, morphology and function, it is imperative to distinguish between the normal physiological impact of body size and the pathological influence of excess fat (Chantler and Lakatta, 2009). Large scaling studies have thoroughly explored the allometric relationship between body size, LV size and dimensions. These studies, however did not address LV function. It was shown that LV size (LVM and LVIDd) related to body size (BSA, BM, height and FFM) in a non-linear fashion, indicating a need for allometric normalisation using allometric scaling before comparing individuals (Batterham and George, 1998, Batterham et al., 1997, de Simone et al., 1992, De Simone et al., 2011). Fat-free mass has been suggested as the most appropriate body size variable to partition out individual differences in body size without masking the impact of excess adipose tissue (Batterham et al., 1997). Indeed, in the context of obesity, scaling LV dimensions to a body size variable that does not incorporate adipose tissue would be the most accurate way of establishing the independent impact of adipose tissue. With regards to LV function, the allometric relationship between body size and SV and CO has previously been reported (de Simone et al., 1997, Turley et al., 2006). Novel TDI- and 2DST-derived measures of LV systolic and diastolic function, their allometric relationships with body size and composition, and whether or not there is a need to scale these measures to body size or composition have not received much attention.

Therefore, the aims of this study is therefore to firstly define the allometric relationship of body size and composition to LV size and function, and establish which LV structural and/or functional variables need to be scaled to body size, notably FFM. Secondly, this study aims to explore the impact of obesity, particularly visceral adiposity and epicardial fat, on LV size,

morphology and function in healthy overweight and obese women using novel echocardiographic techniques and proper scaling techniques.

4.2 Methods

4.2.1 Participants

Eighty five females (age: 35.4 ± 9.1 yrs) were recruited for the study through local poster and email advertisements across the University of Leeds campus. All participants were healthy, free of known cardiovascular disease and were not utilising any form of prescribed medication. The nature and purpose of the study was explained to each participant and written informed consent was provided prior to their participation. Participants represented a broad range of body size categories (BMI range 18.5 – 39.9 kg/m^2).

4.2.2 Experimental protocol

Participants were invited to attend the exercise physiology laboratory at the University of Leeds on a single occasion after being instructed to refrain from heavy physical exercise for 8 hours and have fasted for 12 hours prior to attendance. All anthropometric and echocardiographic variables were measured/calculated at the same visit in a temperature-controlled laboratory following a 5 minute period of rest in the supine position.

4.2.3 Measured variables

The protocols for the following variables are described in detail in the general methods chapter.

4.2.3.1 Anthropometric variables

The anthropometric variables measured/calculated included body mass (BM), height (HT), waist circumference (WC), hip circumference (HC), waist to hip ratio (W:H ratio), fat mass (FM), fat percent (FP) and fat-free mass (FFM).

4.2.3.2 Echocardiographic variables

Echocardiographic techniques are explained in detail in the general methods chapter (section 3.4). Standard 2-D echocardiographic variables included epicardial fat thickness (EFT), left ventricular diastolic internal diameter (LVIDd), diastolic posterior wall thickness (PWTd), diastolic interventricular septal thickness (IVSTd), mean wall thickness (MWT), relative wall

thickness (RWT), left ventricular mass (LVM), ejection fraction (EF), stroke volume (SV). PWD echocardiographic variables included early diastolic inflow velocity (E), late diastolic inflow velocity (A), E:A ratio (E/A), isovolumetric relaxation time (IVRT) and deceleration time (DCT). TDI echocardiographic variables included peak systolic myocardial velocity (Sm), peak early diastolic myocardial velocity (Em), peak late diastolic myocardial velocity (Am), Em:Am and E/Em. Finally, 2DST echocardiographic variables included global longitudinal strain (LongS), global longitudinal systolic and early, late and early to late diastolic strain rates (LongSRs, LongSRe, LongSRa and LongSRe/a respectively), global circumferential strain (CircS), global circumferential systolic and early, late and early to late diastolic strain rates (CircSRs, CircSRe, CircSRa and CircSRe/a respectively), global radial strain (RadS), global radial systolic and early, late and early to late diastolic strain rates (RadSRs, RadSRe, RadSRa and RSRe/a respectively) and LV torsion (LVTor).

4.2.4 Statistical analysis

Statistical analysis procedures are explained in detail in the General Methods chapter (section 3.6). All data were normally distributed and are presented as mean ± SD. The relationships between each pair of anthropometric and echocardiographic variables were checked for linearity using Tanner's "special circumstance" calculation (Tanner, 1949). This involves comparing the correlation coefficient (r,x,y) for each combination of anthropometric and echocardiographic variables with the ratio of the coefficients of variation (CV) for the same two variables (CVx/CVy). Linearity (i.e. when r,x,y is equal to cvx/cvy) was not found between any pair of variables, therefore they were analysed for allometric relationships from natural log transformations of the absolute data. The curvilinear allometric equation of the general form ($y = xb$) was examined as y = dependent variable, x = independent variable and b = the beta exponent of the slope of the log-linear plot. Comparison between the 3 BMI-divided groups was undertaken using a one-way ANOVA for the absolute and allometrically scaled (y/x^{b}) data. Results of all data analysis were considered significant if $P < 0.05$.

4.3 Results

4.3.1 Participants' characteristics

The anthropometric and blood pressure characteristics of the three groups are presented in Table 4.1. The total number of participants was 85, which was divided into three groups according to BMI; normal weight (NW, BMI <25 kg/m^2, n=31), overweight (OW, BMI ≥25 and <30 kg/m^2, n=28) and obese (OB, BMI ≥30 kg/m^2, n=26). Resting blood pressure did not differ between the three groups ($P < 0.05$). All anthropometric and body composition variables except FFM were larger in overweight participants than in their normal weight counterparts ($P < 0.05$), whilst obese participants displayed greater values than both overweight and normal weight participants in all variables except height and waist:hip ratio ($P > 0.05$). In these variables obese participants differed only from normal weight participants ($P < 0.05$).

Table 4. 1 Anthropometric, body composition and blood pressure characteristics for normal weight, overweight and obese participants

	Normal (n=31)	Overweight (n=28)	Obese (n=26)
Age (years)	31.1 ± 8.06	35.5 ± 10.6	40.7 ± 5.31 *†
Weight (kg)	62.2 ± 8.38	75.1 ± 7.37 *	92.8 ± 11.1 *†
Height (m)	1.69 ± 6.41	1.64 ± 6.55 *	164.9 ± 5.53 *
BMI (kg/m^2)	21.7 ± 1.9	27.7 ± 1.46 *	34.1 ± 3.11 *†
BSA (m^2)	1.71 ± 0.14	1.82 ± 0.12 *	1.99 ± 0.14 *†
Fat percent (%)	21.2 ± 5.1	34.7 ± 5.8 *	43.9 ± 2.9 *†
Fat mass (kg)	13.1 ± 3.68	26.4 ± 5.93 *	41.1 ± 6.92 *†
Fat-free mass (kg)	48.7 ± 7.65	47.8 ± 6.26	52.1 ± 4.98 *†
Waist (cm)	75.8 ± 7.89	90.9 ± 9.89 *	105.3 ± 8.66 *†
Waist : Hip	0.80 ± 0.07	0.87 ± 0.07 *	0.87 ± 0.06 *
Epicardial fat (cm)	1.87 ± 0.77	3.46 ± 0.98 *	4.05 ± 1.19 *†
SBP (mmHg)	124 ± 11	127 ± 10	126 ± 9.
DBP (mmHg)	80 ± 5	82 ± 7	84 ± 9

* Significantly different from Normal ($P<0.05$) † significantly different from both Overweight and Normal ($P<0.05$). BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure.

4.3.2 LV size and morphology: relationship to body size and composition

Firstly, Tanner's special circumstances, to test the validity of ratio scaling of LV structural indices by body size indices, were not satisfied in any pair of LV and body size variables. Table 4.2 shows the correlation coefficients (r,x,y) for each combination of anthropometric and echocardiographic structural variables versus the ratio of the coefficients of variation (CV) for the same two variables (CVx/CVy). This eliminates the possibility of a linear relationship between LV structural variables and those of body size and composition. Therefore, allometric log-linear scaling was employed to explore the relationship between LV size and morphology and body size and composition and results are presented in Table 4.3. Figure 4.1 shows the relationship between LVM and BM before and after allometric scaling. After allometric scaling, the correlation coefficient for both variables changed from a significant value of 0.48 to a non-significant value of 0.01 (figure 4.1).

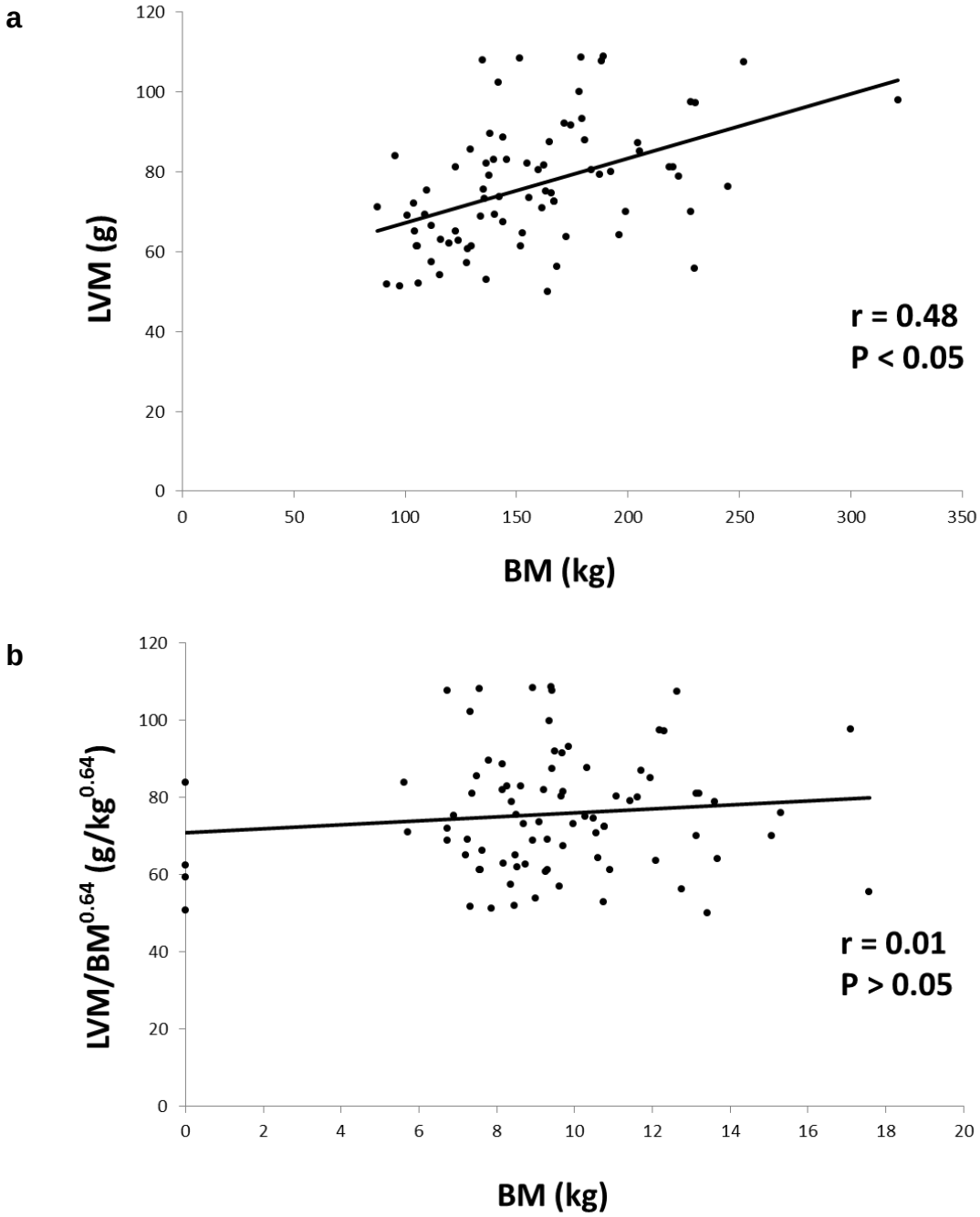

Figure 4. 1 Relationship between LVM and BM before and after allometric scaling

Table 4. 2 Tanner's special circumstances; the correlation coefficients (r,x,y) for each combination of anthropometric and echocardiographic structural variables versus the ratio of the coefficients of variation for the same two variables (between brackets)

	BSA	BM	HT	FM	FFM	WC	EFT
LVM	0.46 (0.35)	0.48 (0.74)	0.10 (0.14)	0.39 (1.78)	0.43 (0.49)	0.48 (0.60)	0.40 (1.6)
LVIDd	0.01 (0.93)	0.07 (1.96)	0.17 (0.37)	0.23 (4.76)	0.28 (1.28)	0.19 (1.61)	0.28 (4.26)
LVL	0.27 (0.62)	0.27 (0.92)	0.10 (1.35)	0.26 (1.18)	0.17 (0.75)	0.30 (0.65)	0.33 (0.22)
IVSTd	0.19 (0.03)	0.24 (0.06)	0.07 (0.01)	0.27 (0.14)	0.06 (0.037)	0.30 (0.05)	0.26 (0.12)
PWTd	0.18 (0.32)	0.24 (0.66)	0.12 (0.13)	0.30 (1.63)	0.07 (0.44)	0.34 (0.55)	0.42 (1.47)

LVM, left ventricular mass; EDV, end-diastolic volume, LVIDd, left ventricular diastolic internal diameter; LVL, left ventricular length; IVSTd, diastolic interventricular septum thickness; PWTd, diastolic posterior wall thickness.

Table 4. 3 The allometric correlation (r) and allometric power exponent (*b* ± 95% confidence intervals) for LV morphology and indices of body size and composition

	BSA	BM	HT	FM	FFM	WC	EFT
LVM	0.46 ** (1.3±0.58)	0.48 ** (0.64±0.27)	0.10 (0.7±1.62)	0.39 ** (0.19±0.1)	0.43 ** (0.92±0.45)	0.48 ** (0.75±0.31)	0.40 ** (28.8±17.2)
LVIDd	-0.01 (-0.02±0.25)	- 0.07 (-0.04±0.12)	0.17 (0.5±1.07)	- 0.23 * (-0.05±0.04)	0.28* (0.23±0.18)	- 0.19 (-0.12±0.15)	-0.28 * (-0.26±0.21)
LVL	0.27 * (0.74±0.62)	0.27 * (0.35±0.3)	0.10 (0.07±2.23)	0.26 * (0.13±0.11)	0.17 (0.37±0.49)	0.30 * (0.49±0.35)	0.33 * (1.15±0.86)
IVSTd	0.19 † (0.28±0.24)	0.24 * (0.29±0.25)	-0.07 (-0.99±5.05)	0.27 * (0.27±0.22)	0.06 (0.25±0.95)	0.30 * (0.92±0.7)	0.26 * (0.28±0.24)
PWTd	0.18 † (0.57±0.73)	0.24 * (0.37±0.34)	-0.12 (-0.1±2.9)	0.30 * (0.16±0.12)	-0.07 (-0.02±0.58)	0.34 ** (0.58±0.39)	0.42 ** (0.26±0.13)
MWT	0.43 ** (0.98±0.47)	0.48 ** (0.52±0.21)	- 0.01 (-0.08±1.33)	0.49 ** (0.20±0.09)	0.23 * (0.39±0.38)	0.56 ** (0.71±0.24)	0.53 ** (0.27±0.13)
RWT	0.34 ** (0.99±0.63)	0.40 ** (0.56±0.29)	- 0.08 (-0.58±1.7)	0.46 ** (0.24±0.1)	0.07 (0.16±0.51)	0.50 ** (0.82±0.32)	0.51 ** (0.13±0.06)

* P < 0.05, ** < 0.005, LVM, † < 0.09. LVM, left ventricular mass; EDV, end-diastolic volume, LVIDd, left ventricular diastolic internal diameter; LVL, left ventricular length; IVSTd, diastolic interventricular septum thickness; PWTd, diastolic posterior wall thickness; MWT, mean wall thickness; RWT, relative wall thickness.

4.3.2.1 LV size

Generally, larger body sizes were associated with bigger, heavier and longer left ventricles as shown by the significant correlation of both LVM and LVL with BSA. Height was not related to either LVM or LVL ($P > 0.05$). Hence the relationship to body size was primarily as a result of BM. Furthermore, both LVM and LVL significantly correlated with FM, WC and EFT, whereas only LVM significantly correlated with FFM ($P < 0.05$). There was no relationship between LVIDd and body size variables BM, HT and BSA. However, with regards to body composition, LVIDd exhibited opposite relationships with adipose and non-adipose tissue, showing a modest but significant positive correlation with FFM and negative correlation with FM, WC and EFT.

4.3.2.2 LV morphology

Generally, larger body sizes were associated with thicker LV walls as shown by the significant correlation between both LVM and mean wall thickness (MWT) and BM, and subsequently, BSA. Furthermore, there was a significant correlation between RWT and both BM and BSA, both of which did not correlate with LVIDd, suggesting a concentric LV morphology associated with bigger body sizes. Looking more closely at body composition, FM and FFM each were associated with different LV morphologies. FM significantly and positively correlated with MWT and RWT and negatively with LVIDd. However, FFM exhibited a significant positive correlation with both MWT and LVIDd with no correlation with RWT. This indicates a concentric LV morphology associated with higher adipose tissue content as opposed to an eccentric LV morphology with higher non-adipose tissue content. The correlations of LV morphology with FFM were modest ($r = 0.20$ to 0.30) compared to FM ($r > 0.46$). Furthermore, LVM, MWT, RWT significantly and positively correlated with WC and EFT whereas LVID negatively correlated with WC and EFT, though only reaching statistical significance with EFT. Finally, EFT exhibited the strongest correlations ($r > 0.50$) with indices of LV size and morphology compared to all other indices of body size and composition.

4.3.2.3 LV size and morphology vs body size and composition: what is the nature of the relationship?

Generally, the allometric power exponents generated for the indices of LV size and morphology scaled for body size and composition confirmed a non-linear relationship between them, and were not always fitting with the theory

of geometric similarity (table 4.3). Indeed, the allometric *b* exponent for LVM (3-dimensional) scaled for BSA (2-dimensional) included 1.5 in its 95% confidence intervals. However, the allometric *b* exponent for LVM (3-dimensional) scaled to BM (3-dimensional) was lower than and did not include 1.0 within its 95% confidence intervals (95%CI). As for one-dimensional measurements of LV, when scaled to BSA (2-dimensional) and BM (3-dimensional), the generated power exponents did include 0.5 and 0.33 respectively within their 95% CI. Similarly, the generated allometric *b* exponents for LVM (3-dimensional), LVID and MWT (both 1-dimensional) scaled to FFM (3-dimensional) included 1.0 and 0.33 respectively within their respective 95% CI.

However, scaling indices of LV size and morphology to measures of adipose tissue (FM, WC and EFT) generated *b* exponents that were low, not fitting with the theory of geometric similarity and with broad 95% CI.

4.3.3 Does LV size and morphology differ between normal weight, overweight and obese subjects?

The absolute mean values ± SD of the echocardiographic measurements of LV size and morphology before and after allometric scaling for indices of body size and composition for the 3 groups are shown in Table 4.4.

In absolute terms overweight and obese participants did not differ from each other in indices of LV size ($P > 0.05$). However both groups displayed significantly greater LVM and wall thicknesses than the normal weight participants ($P < 0.05$). The mean LVM values for all 3 groups did not exceed the limits of normal according the ASE guidelines (Lang et al., 2005). Whilst the overweight and obese participants had smaller LVIDd than their normal weight counterparts, the diameters fell within the normal range. After removing the influence of BM and BSA the differences in LV size between the three groups disappeared. Interestingly, after scaling for FFM, the OB group's LVM remained significantly greater than the NW group, however the difference between both groups' mean LVM decreased from ~30% before scaling to ~19% after scaling. Figure 4.2 represents the differences between the 3 groups' LVM before and after allometric scaling for BSA and FFM.

With regards to LV morphology, the NW group had normal average MWT and RWT as opposed to the OW and OB groups who both had significantly greater average MWT and RWT exceeding the limits for concentric remodelling. There was no significant difference between both groups.

Allometric scaling of MWT and RWT for FM and WC resulted in removal of the differences between the 3 groups, whereas scaling for BM, BSA and FFM did not remove the differences between the 3 groups.

Table 4. 4 Difference between normal weight, overweight and obese subjects in LV size and morphology

	Normal	Overweight	Obese
LVM (g)	136.7±31.6	158.6±42.6 *	178.3±47.7 *
$LVM/BM^{0.64}$	9.81±2.38	10±2.58	9.81±2.48
$LVM/BSA^{1.3}$	80.5±19.3	87.2±23	89.3±22.8
$LVM/FFM^{0.92}$	2.85±0.69	3.18±0.85	3.38±0.83 *
$LVM/FM^{0.19}$	84.2±21.1	81.4±19.9	87.2±22.9
LVIDd (cm)	4.73±0.36	4.36±0.53 *	4.48±0.47 *
$LVIDd/FFM^{0.23}$	1.95±0.15	1.78±0.20 *	1.82±0.16 *
$LVIDd/FM^{-0.05}$	5.38±0.41	5.12±0.61	5.44±0.56
LVL (cm)	5.75±1.73	6.83±1.86 *	6.46±1.28
$LVL/BM^{0.35}$	1.35±0.39	1.51±0.4	1.34±0.3
$LVL/BSA^{0.27}$	3.37±0.95	3.74±0.97	3.29±0.81
$LVL/FM^{0.13}$	4.11±1.22	4.43±1.22	3.96±0.82
$LVL/WC^{0.49}$	0.69±0.2	0.74±0.2	0.66±0.15
MWT (cm)	0.84±0.13	1.05±0.25 *	1.10±0.22 *
$MWT/BM^{0.52}$	0.098±0.016	0.110±0.025 *	0.105±0.022
$MWT/BSA^{0.43}$	0.50±0.08	0.58±0.13 *	0.55±0.11 *
$MWT/FFM^{0.29}$	0.19±0.03	0.23±0.05 *	0.23±0.04 *
$MWT/FM^{0.20}$	0.51±0.09	0.53±0.12	0.51±0.09
RWT	0.36±0.07	0.49±0.16 *	0.50±0.13 *
$RWT/BM^{0.56}$	0.036±0.007	0.044±0.013 *	0.040±0.011
$RWT/BSA^{0.43}$	0.21±0.04	0.27±0.08 *	0.25±0.07 *
$RWT/FM^{0.24}$	0.19±0.01	0.22±0.06	0.20±0.05

* Significant difference from NW group. LVM, left ventricular mass; LVIDd = left ventricular diastolic internal diameter; LVL, left ventricular length; MWT, mean wall thickness; RWT, relative wall thickness; BM, body mass; BSA, body surface area; FFM, fat-free mass; FM, fat mass; WC, waist circumference.

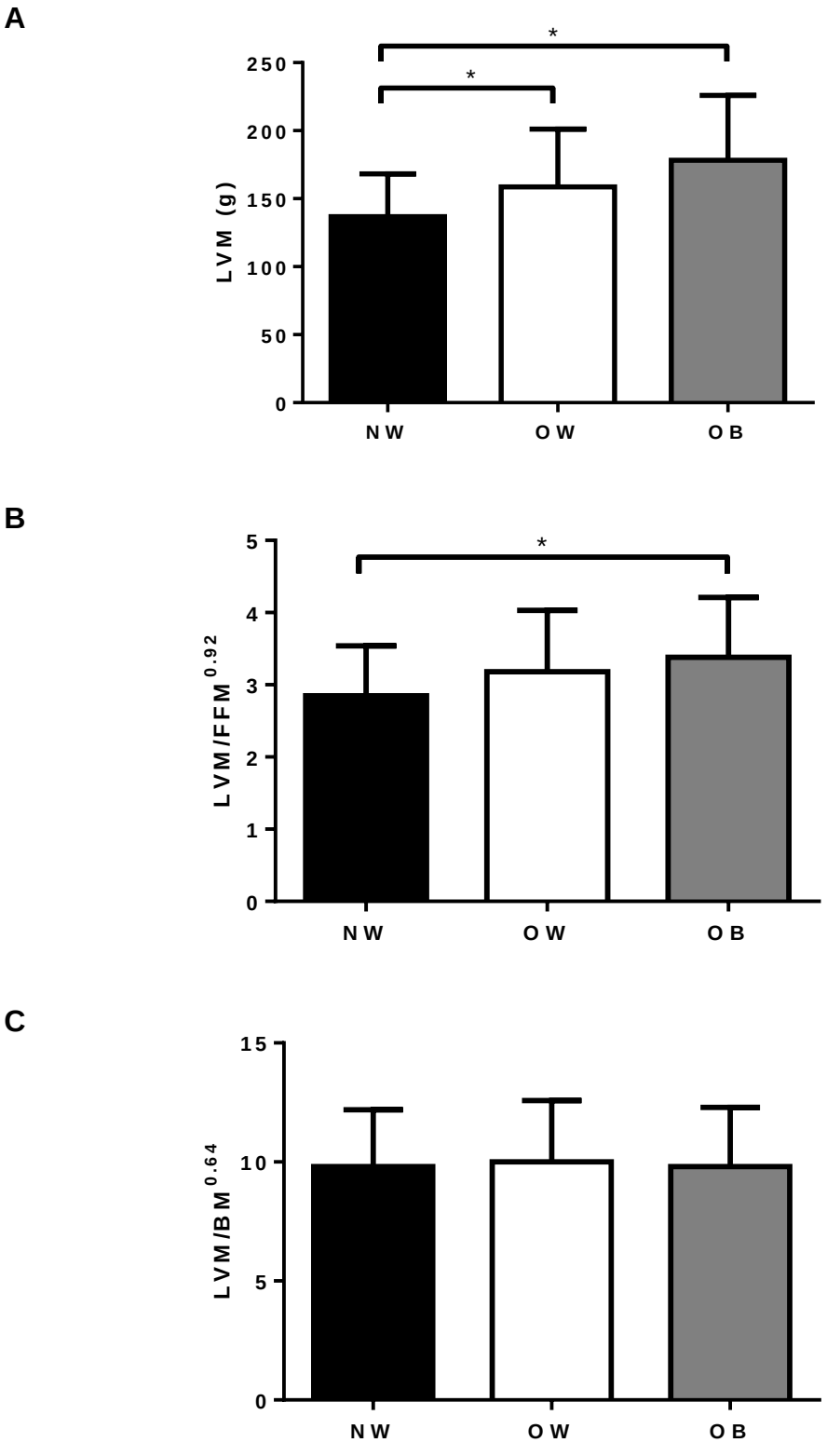

Figure 4. 2 Left ventricular mass in normal weight (NW), overweight (OW) and obese (OB) women before and after allometric scaling for body size or fat-free mass. * indicates significant difference.

4.3.4 LV systolic function vs body size and composition

The allometric correlations (r) and power exponents (*b*) of the measures of LV systolic function vs. body size and composition are presented in Tables 4.5 and 4.6. Stroke volume exhibited significant positive non-linear correlations with BSA, BM, FFM, WC and EFT ($P < 0.05$), the strongest being with FFM ($r = 0.33$, *b*: 0.67 ± 0.45). This indicates a need to normalise SV for FFM in order to properly assess the impact of excess adipose tissue on stroke volume without the influence of non-adipose tissue. The 95% confidence intervals for the allometric power exponents generated for SV scaled for FFM included 1.0 which is consistent with the theory of geometric similarity as both measures are 3-dimensional.

Longitudinal strain negatively correlated with FM, WC and EFT, the strongest correlation with EFT ($r = -0.33$, $P < 0.05$). Interestingly, only EFT correlated negatively with longitudinal SRs and positively with circumferential SRs. None of the remaining systolic variables correlated with body size or FFM.

Table 4. 5 The allometric correlations (r) and allometric power exponents (*b* ± 95% confidence intervals) for standard and TDI-derived LV systolic function and indices of body size and composition

	BSA	BM	HT	FM	FFM	WC	EFT
SV	0.28 * (0.75±0.6)	0.26 * (0.34±0.29)	0.14 (0.97±1.54)	0.21 (0.10±0.11)	0.33 * (0.67±0.45)	0.28 * (0.43±0.34)	0.29 * (0.15±0.12)
EF	0.04 (0.05±0.33)	0.08 (0.06±0.16)	0.12 (-0.42±0.82)	0.17 (0.05±0.07)	0.14 (-0.15±0.25)	0.19 (0.16±0.19)	0.20 † (0.05±0.06)
FS	0.04 (-0.07±0.44)	0.00 (0.01±0.21)	0.14 (-0.67±1.1)	0.00 (0.00±0.09)	0.01 (0.01±0.04)	0.06 (0.07±0.25)	0.13 (0.05±0.09)
Sm	0.09 (-0.19±0.44)	0.08 (-0.07±0.19)	0.09 (-0.45±1.09)	0.02 (-0.01±0.08)	0.08 (-0.11±0.34)	0.03 (0.03±0.26)	-0.04 (-0.02±0.01)

* $P < 0.05$. † $P < 0.09$. SV, stroke volume; EF, ejection fraction; FS, fractional shortening; SWS, systolic wall stress; Sm, systolic myocardial velocity.

Table 4. 6 The allometric correlations (r) and allometric power exponents (*b* ± 95% confidence intervals) for 2DST-derived LV systolic function and indices of body size and composition

LongS	0.19 (-0.32±0.47)	0.25 (-0.21±0.22)	0.12 (0.46±1.07)	0.29 * (-0.09±0.08)	0.01 (-0.01±0.39)	0.29 * (-0.27±0.26)	- 0.33 * (-0.13±0.1)
CircS	0.02 (-0.06±0.96)	0.08 (-0.12±0.45)	0.15 (1.1±2.07)	0.09 (-0.05±0.15)	0.10 (0.25±0.71)	0.14 (-0.28±0.57)	-0.17 (-0.12±0.18)
RadS	0.05 (-1.28±2.2)	0.09 (-0.65±1.27)	0.12 (-2.74±4.76)	0.02 (-0.03±0.71)	0.21 (-0.86±1.4)	0.05 (0.21±1.58)	0.24 † (0.33±0.35)
LongSRs	0.13 (-0.17±0.35)	0.08 (-0.05±0.17)	0.17 (-0.47±0.75)	0.02 (-0.00±0.06)	0.12 (-0.11±0.26)	0.03 (-0.02±0.2)	- 0.28 * (-0.08±0.08)
CircSRs	0.25 * (1.13±1.24)	0.25 * (0.53±0.59)	0.09 (0.87±2.79)	0.25 (0.18±0.20)	0.14 (0.45±0.94)	0.14 (0.39±78)	0.30 * (0.27±0.25)
RadSRs	0.09 (-0.27±1.16)	0.06 (-0.09±0.66)	0.15 (-0.92±3.26)	0.02 (-0.03±0.82)	0.02 (-0.03±0.82)	0.06 (-0.11±0.82	0.13 (0.09±0.09)

* $P < 0.05$. † $P < 0.09$. LongS, longitudinal strain; CircS, circumferential strain; RadS, radial strain; LongSRs, longitudinal systolic strain rate; CircSRs, circumferential systolic strain rate, RadSRs, radial systolic strain rate.

4.3.5 LV systolic function: is there a difference between normal weight, overweight and obese participants?

Table 4.7 presents the absolute values (mean ± SD) of LV systolic function in the 3 groups. SV, absolute and scaled for FFM, did not differ significantly between the 3 groups. Longitudinal strain was significantly lower in the obese compared to both the normal weight and overweight subjects, and no difference was found between these two groups. No significant difference was found between the 3 groups' systolic haemodynamic parameters, myocardial velocity, circumferential and radial deformation or torsion.

Table 4. 7 LV systolic function in normal weight, overweight and obese participants

	Normal	Overweight	Obese
SV (ml)	50.4 ± 13.9	54.9 ± 15	53.2 ± 10.4
$SV/FFM^{0.67}$ ($ml/g^{0.67}$)	3.76 ± 0.89	4.07 ± 1.18	3.8 ± 0.76
EF (%)	61.6 ± 7.45	65.4±10.8	63.6 ± 7
FS	0.37 ± 0.06	0.37 ± 0.07	0.38 ± 0.08
Sm (ms)	6.32 ± 1.16	6.54 ± 1.55	6.16 ± 1.02
LS (%)	22.1 ± 2.95	21 ± 2.75	19 ± 2.72 *†
CS (%)	18.6 ± 4.8	17.1 ± 4.72	16.3 ± 5.34
RS (%)	45.67 ± 19.3	45.16 ± 21.6	44.5 ± 20.5
LSRs (sec^{-1})	1.07 ± 0.13	1.07 ± 0.11	1.05 ± 0.13
CSRs (sec^{-1})	0.93 ± 0.23	1.27 ± 0.68	1.19 ± 0.57
RSRs (sec^{-1})	2.32 ± 0.51	2.16 ± 0.4	2.19 ± 0.59
Torsion (%)	19.14 ± 7.2	18.57 ± 7.64	15.3 ± 5.3

* indicates significantly different from Normal ($P < 0.05$). † significantly different from Overweight ($P < 0.05$). SV, stroke volume; FFM, fat-free mass; EF, ejection fraction; FS, fractional shortening; SWS, systolic wall stress; Sm, systolic myocardial velocity; LongS, longitudinal strain; CircS, circumferential strain; RadS, radial strain; LongSRs, longitudinal systolic strain rate; CircSRs, circumferential systolic strain rate; RadSRs, radial systolic strain rate.

4.3.6 LV diastolic function vs. body size and composition

The allometric relationships between the measures of LV diastolic function and body size and composition are presented in Tables 4.8, 4.9 and 4.10. Generally, increasing degrees of body size were associated with reductions in LV diastolic function. Body surface area and BM, correlated negatively with E/A, Em, Em/Am and LongSRe/a and positively with A, IVRT, Am and LongSRa. These correlations were stronger with BM than BSA and were mediated by the adipose tissue component of BM rather than the muscular component. Indeed, all of the above mentioned variables of LV diastolic function displayed similar correlation patterns with FM, WC and EFT and no significant correlations were found with FFM. Waist circumference had the strongest correlations with measures of LV diastolic function (r values ranging from ~0.50 to ~0.60) as shown in table 4.6. Interestingly, CircSRe, CircSRa, RadSRe and RadSRe/a all positively correlated with BSA, BM, FM, WC and EFT. Relationships between LV diastolic functional measures and FFM have generally been non-significant. Additionally, the generated allometric power exponents were small with very broad 95% confidence intervals. Circumferential SRa was the only variable to correlate modestly (r = 0.38) with FFM, however this was an isolated finding and does not provide substantial evidence as to the need to normalise LV diastolic strain rate to FFM. Additionally, the generated allometric power exponent very broad 95% confidence intervals (0.4 to 2.36) indicating an unstable and weak relationship.

Table 4. 8 The allometric correlations (r) and allometric power exponents (*b* ± 95% confidence intervals) for PWD-derived LV diastolic function and indices of body size and composition

	BSA	BM	HT	FM	FFM	WC	EFT
E	0.04 (-0.07±0.43)	0.10 (-0.09±0.20)	0.18 (0.86±1.06)	0.19 (-0.07±0.08)	0.10 (0.15±0.34)	0.13 (-0.15±0.25)	-0.05 (0.02±0.08)
A	0.43 * (1.29±0.61)	0.50 * (0.69±0.27)	0.06 (-.47±01.66)	0.52 * (0.27±0.11)	0.22 (0.49±0.05)	0.55 * (0.92±0.33)	0.55 ** (0.31±0.29)
E/A	0.36 * (-1.25±0.72)	0.45 * (-0.73±0.32)	0.14 (1.25±1.92)	0.52 * (-0.32±0.12)	0.12 (-0.31±0.60)	0.53 * (-1.05±0.38)	-0.46 ** (-0.31±0.13)
DCT	0.10 (0.40±0.88)	0.05 (0.09±0.72)	0.20 (2±2.17)	0.06 (-0.04±0.16)	0.29 * (0.88±0.46)	0.08 (0.18±51)	-0.05 (-0.03±0.17)
IVRT	0.15 (0.52±0.77)	0.23 * (0.37±0.36)	0.19 (-1.63±1.95)	0.28 * (0.16±0.13)	0.03 (-0.08±0.59)	0.25 * (0.46±0.43)	0.39 ** (0.25±0.14)

* P < 0.05. E; early diastolic inflow velocity, A; late (atrial phase) diastolic inflow velocity, DCT; deceleration time, IVRT; isovolumetric relaxation time.

Table 4. 9 The allometric correlations (r) and allometric power exponents (*b* ± 95% confidence intervals) for TDI-derived LV diastolic function and indices of body size and composition

	BSA	BM	HT	FM	FFM	WC	EFT
Em	0.28 * (-0.61±0.5)	0.36 * (-0.37±0.27)	0.11 (0.55±1.36)	0.44 * (-0.16±0.09)	0.00 (-0.01±0.45)	0.47 * (-0.64±0.33)	-0.36 ** (-0.16±0.12)
Am	0.25 * (0.56±0.6)	0.31 * (0.33±0.28)	0.07 (-0.36±1.39)	0.33 * (0.12±0.1)	0.02 (0.03±0.46)	0.53 * (0.72±0.33)	0.25 † (0.11±0.22)
Em/Am	0.31 * (-1.16±1.01)	0.40 * (-0.70±0.46)	0.13 (1.04±2.3)	0.47 * (-0.28±0.16)	0.01 (0.03±0.79)	0.61 * (-1.35±0.52)	-0.37 ** (-0.27±0.2)
E/Em	0.13 (0.33±0.7)	0.13 (0.14±0.32)	0.06 (0.33±1.66)	0.12 (0.05±0.12	0.05 (0.1±0.58)	0.19 (0.28±0.42)	0.17 (0.08±0.13)

* P < 0.05. A; late (atrial phase) diastolic inflow velocity, Em; early diastolic myocardial velocity, Am; late (atrial phase) diastolic myocardial velocity, E; early diastolic inflow velocity.

Table 4. 10 The allometric correlations (r) and allometric power exponents (*b* ± 95% confidence intervals) for 2DST-derived LV diastolic function and indices of body size and composition

	BSA	BM	HT	FM	FFM	WC	EFT
LongSRe	0.09 (-0.24±0.73)	0.09 (-0.11±0.35)	0.03 (-0.18±1.65)	0.16 (-0.07±0.12)	0.05 (0.09±0.55)	0.10 (-0.16±0.46)	-0.31 * (-0.16±0.14)
CircSRe	0.32 * (1.17±0.97)	0.42 * (0.72±0.44)	0.17 (-1.43±2.41)	0.49 * (0.29±0.15)	0.05 (0.13±0.77)	0.41 * (0.94±0.59)	0.44 ** (0.32±0.18)
RadSRe	0.25 (0.96±1.07)	0.32 * (0.62±0.52)	0.08 (-0.67±2.38)	0.35 * (0.27±0.19)	0.00 (0.01±0.79)	0.32 * (0.74±0.63)	0.17 (0.13±0.22)
LongSRa	0.31 * (0.68±0.59)	0.47 * (0.49±0.26)	0.35 * (-1.7±1.32)	0.59 * (0.21±0.08)	0.09 (-0.14±0.47)	0.52 * (0.71±0.33)	0.34 * (0.15±0.12)
CircSRa	0.40 * (1.86±1.23)	0.41 * (0.89±0.58)	0.12 (1.32±3.17)	0.29 * (0.23±0.22)	0.38 * (1.38±0.98)	0.40 * (1.11±0.75)	0.14 (0.14±0.28)
RadSRa	0.07 (-0.31±1.47)	0.10 (-0.23±0.71)	0.06 (0.62±3.14)	0.04 (-0.04±0.27)	0.04 (-0.15±1.14)	0.05 (-0.12±0.78)	0.03 (0.02±0.32)

* P < 0.05. LongSRe; longitudinal early diastolic strain rate, CircSRe; circumferential early diastolic strain rate, RadSRe; radial early diastolic strain rate, LongSRa: longitudinal late (atrial phase) diastolic strain rate, CircSRa; circumferential late (atrial phase) diastolic strain rate, RadSRa: radial late (atrial phase) diastolic strain rate.

4.3.7 LV diastolic function: is there a difference between normal weight, overweight and obese participants?

Tables 4.11 and 4.12 present the values (mean ± SD) of absolute and allometrically scaled LV diastolic function in normal weight, overweight and obese subjects. Both overweight and obese subjects exhibited poorer LV diastolic function compared to their normal-weight counterparts. This was demonstrated by significantly higher A, IVRT, Am (obese group only) and LongSRa and lower E/A, Em/Am and longSRe/a. However, both overweight and obese subjects had significantly higher CircSRe, RadSRe and RadSRe/a than normal-weight women. The only variable that was significantly higher in the obese compared to the overweight group was RadSRe. Interestingly, all these measures became non-significantly different between the 3 groups after they were allometrically scaled to BSA and BM. Finally, E velocity, DCT and E/Em were similar in the 3 groups.

Table 4. 11 Standard PW- and TDI-derived echocardiographic measures of LV diastolic function in normal weight, overweight and obese women before and after allometric scaling for body size

	Normal	Overweight	Obese
E (ms)	94.1 ± 18.3	87.7 ± 14.5	87 ± 14.7
A (ms)	45.6 ± 13.1	56.9 ± 11.7 *	61.3 ± 14.3 *
$A/BSA^{1.29}$	23.4 ± 5.2	24.8 ± 6.8	22.4 ± 5.7
$A/BM^{0.69}$	2.67 ± 0.58	2.77 ± 0.74	2.53 ± 0.65
E/A	2.11 ± 0.66	1.61 ± 0.43 *	1.48 ± 0.51 *
DcT (ms)	198.3 ± 70.2	172.1 ± 52.1	191.3 ± 67
IVRT (ms)	79.5 ± 8.3	115.4 ± 53 *	104.2 ± 39.9 *
$IVRT/BM^{0.37}$	17.7 ± 1.9	18.3 ± 4.4	18 ± 3.4
Em (ms)	8.83 ± 0.96	7.55 ± 1.19 *	7.25 ± 1.6 *
$Em/BSA^{-0.61}$	11.8 ± 1.5	11.7 ± 2.4	12.2 ± 1.6
$Em/BM^{-0.37}$	39.6 ± 4.7	39.2 ± 7.5	40.9 ± 4.7
Am (ms)	6.31 ± 1.16	6.99 ± 1.31	7.68 ± 1.26 *
$Am/BSA^{0.56}$	4.58 ± 0.99	5.07 ± 0.95	4.68 ± 0.92
$Am/BM^{0.33}$	1.56 ± 0.34	1.74 ± 0.33	1.6 ± 0.31
Em/Am	1.42 ± 0.37	1.13 ± 0.27 *	1.02 ± 0.43 *
E/Em	10.4 ± 3.6	11.5 ± 2.1	12.3 ± 2.9

* indicates significantly different from Normal ($P < 0.05$). † significantly different from Overweight ($P < 0.05$). E, early diastolic inflow velocity; A, late (atrial phase) diastolic inflow velocity; DCT, deceleration time; IVRT, isovolumetric relaxation time; Em, early diastolic myocardial velocity; Am, late (atrial phase) diastolic myocardial velocity.

Table 4. 12 2DST-derived longitudinal, circumferential and radial diastolic strain rate in normal weight, overweight and obese women before and after allometric scaling for body size

	Normal	Overweight	Obese
LongSRe (sec^{-1})	1.54 ± 0.35	1.41 ± 0.35	1.42 ± 0.32
CircSRe (sec^{-1})	1.00 ± 0.35	1.35 ± 0.4 *	1.42 ± 0.33 *
CircSRe/$BSA^{1.17}$	0.55 ± 0.15	0.66 ± 0.21	0.56 ± 0.16
CircSRe/$BM^{0.72}$	0.05 ± 0.01	0.06 ± 0.02	0.05 ± 0.01
RadSRe (sec^{-1})	1.19 ± 0.32	1.79 ± 0.64 *	2.35 ± 0.76 *†
RadSRe/$BM^{0.62}$	0.12 ± 0.03	0.10 ± 0.03	0.11 ± 0.04
LongSRa (sec^{-1})	0.72 ± 0.1	0.89 ± 0.16 *	0.95 ± 0.17 *
LongSRa/$BSA^{0.31}$	0.62 ± 0.07	0.72 ± 0.16	0.63 ± 0.10
Long SRa/$BM^{0.47}$	0.10 ± 0.01	0.12 ± 0.02	0.10 ± 0.02
CircSRa (sec^{-1})	0.49 ± 0.13	0.57 ± 0.27 *	0.68 ± 0.35 *
CircSRa/$BSA^{1.86}$	0.17 ± 0.03	0.21 ± 0.09	0.20 ± 0.07
CircSRa/$BM^{0.89}$	0.01 ± 0.00	0.01 ± 0.01	0.01 ± 0.00
RadSRa (sec^{-1})	1.33 ± 0.84	1.37 ± 0.73	1.12 ± 0.67
LongSRe/a	2.21 ± 0.69	1.63 ± 0.46 *	1.55 ± 0.47 *
CircSRe/a	2.06 ± 0.82	2.65 ± 1.11	2.61 ± 0.72
RadSRe/a	0.97 ± 0.31	1.76 ± 1.1 *	1.74 ± 0.63 *

* significantly different from Normal ($P < 0.05$). † significantly different from Overweight ($P < 0.05$). LongSRe, early diastolic longitudinal strain rate; CircSRe, early diastolic circumferential strain rate; RadSRe, early diastolic radial strain rate; LongSRa, late (atrial phase) diastolic longitudinal strain rate; CircSRa, late (atrial phase) diastolic circumferential strain rate; RadSRa, late (atrial phase) diastolic radial strain rate; BSA, body surface area; BM, body mass.

4.4 Discussion

The principal findings of this study were that LV size and morphology relate to overall body size and composition in a non-linear fashion. Furthermore, scaling LVM to BSA or BM, even allometrically, results in over-correction for body size as it removes the impact of adipose as well as non-adipose tissue, leading to the underestimation of LVM in overweight and obese subjects. Scaling to FFM successfully partitions out individual differences in non-adipose tissue size and allows the identification of the impact of excess adipose tissue on LV size. This study also shows that excess visceral fat is associated with concentric as opposed to eccentric LV hypertrophy. Moreover, LV functional indices did not correlate with FFM, ruling out the need for normalisation prior to comparison between groups. This study shows that obesity is associated with more pronounced diastolic than systolic dysfunction, the latter being fairly subtle and only detected by novel 2DST echocardiography. Finally, this study identified for the first time an association between excess epicardial fat thickness and reduced LV systolic myocardial deformation in healthy obese women, not associated with excess body fat or abdominal visceral fat, pointing to a possible mechanical impact of epicardial fat on LV systolic function.

4.4.1 Impact of body size and composition and excess adiposity on LV size and morphology

Generally, a positive correlation was found between overall LV size and body size confirming the already established notion that obesity is associated with LV hypertrophy. However, this relationship was non-linear as indicated by the absence of Tanner's special circumstance between each pair of LV size vs. body size. Allometric scaling was therefore used as adopting the ratio scaling technique to compare individuals of different sizes would have been inappropriate.

The generated allometric power exponents for LVM scaled to body size and composition further confirmed the non-linear association and were similar to values previously reported by Batterham (Batterham and George, 1998, Batterham et al., 1997). As explained by Batterham, theoretically the relationship between LV and body dimensions should follow the theory of geometric similarity, ie. LVM (3-dimensional) should scale to BM (3-dimensional) to the power of 1.0, to height (1-dimensional) to the power of 3.0 and to BSA (2-dimensional) to the power of 1.5. Similarly, LVID (1-

dimensional) should scale to BM (3-dimensional) to the power of 0.33, to height to the first power and to BSA (2-dimensional) to the power of 0.5 (Batterham et al., 1999). In this study, the theory of geometric similarity did not apply with all body size and composition variables.

With regards to body size variables (ie. BM, height and BSA), the generated allometric exponent for LVM scaled to BSA followed the dimensionality theory. However this was not the case when scaled to BM or height. Indeed, LVM scaled to BSA to a power exponent of 1.3 ($P < 0.05$) which is not significantly different from 1.5 and included it in the 95% CI. When LVM was scaled to BM, the generated allometric exponent was 0.64 ($P < 0.05$) which is significantly lower than 1.0 and not within the 95%CI. This finding is in line with a previous study by (Batterham et al., 1997) reporting an allometric exponent of 0.78. This appears to be secondary to the adipose tissue component of BM as we show that the allometric exponent for LVM scaled to FM is 0.19 ($P < 0.05$) which is significantly lower than 1.0 and does not include it in the 95%CI. In contrast, the allometric exponent for LVM scaled to FFM was 0.92 ($P < 0.05$) which is not significantly different from 1.0 and included it in the 95% CI. This indicates that LVM increases with increasing adipose tissue to a lesser rate than it does with muscle tissue. Therefore, the scaling exponent of LVM to BM will reduce with increasing adipose tissue content. This is in contrast to previous reports by (Batterham and George, 1998) showing no significant correlation between LVM and FM and suggested that the influence of fat on LV hypertrophy is negligible. However, their studies consisted of young healthy non-obese men and women with an average body fat content of ~22% as opposed to our cohort which included overweight and obese subjects with body fat of up to ~45%. In the Strong Heart Study, a significant correlation between LVM and FM was reported in a population of healthy obese men and women which is in line with our findings (Bella et al., 1998). Interestingly, we did not observe any significantly correlation between HT and both LVM or LVIDd ($P > 0.05$) and the generated allometric exponents were not significantly different from zero. This may be due to the limited range of heights in our cohort. Previous studies showed a significant correlation between HT and both LVM and LVIDd with allometric exponents not significantly different from predicted values by the dimensionality theory. Batterham reported an allometric exponent of 0.63 for LVIDd scaled to HT, and 1.0 was included in the 95%CI (Batterham and George, 1998). However the allometric power exponent for LVM scaled to HT reported by different studies has been variable. (de Simone et al., 1992) reported a value 2.7, whereas (Chirinos et al., 2010,

Daniels et al., 1995) reported values of 1.7 and 3.0 respectively. This indicates the necessity of using sample-specific allometric power exponents in all studies where scaling is needed, as was suggested by Batterham (Batterham et al., 1997). In this study we show that LVIDd does not correlate with BM or BSA which contradicts reports by (Batterham et al., 1998). This appears to be due to the observed opposite influences of both adipose and non-adipose tissue on LVIDd, as will be explained below.

With regards to body composition, the theory of geometric similarity applied only with FFM as the allometric exponents for LVM and LVIDd scaled to FFM were 0.92 and 0.23 respectively ($P < 0.05$). These values are fairly close to the values predicted by the dimensionality theory (1.0 and 0.33 respectively) both of which were included in the 95% CI. Similar values were previously reported by (Batterham et al., 1997) and (Batterham and George, 1998). However, as mentioned above the allometric exponent for LVM scaled to FM was 0.19 ($P < 0.05$). LVIDd negatively correlated with FFM and the generated allometric exponent was -0.05 ($P < 0.05$) and zero was not included in the 95% CI. The fact that LVIDd correlated positively with FM and negatively with FFM could explain the lack of correlation with BM and BSA as the two opposite impacts of adipose and muscle mass would have eliminated one another when combined into one body size variable. This contradicts previous reports by (Bella et al., 1998) showing a positive correlation between LVIDd and FM.

On group comparison, normalizing LVM for $FFM^{0.92}$, appropriately partitioned out the individual differences in non-adipose tissue content and strictly identified the impact of obesity on LV size by showing significantly larger $LVM/FFM^{0.92}$ in the overweight and obese females. However, normalising for $BM^{0.64}$ or $BSA^{1.3}$ resulted in all 3 groups having non-significantly different $LVM/BM^{0.64}$ and $LVM/BSA^{1.3}$. Therefore, when comparisons between subjects of different body sizes is to be carried out, LV size should be allometrically scaled to FFM and not BM or BSA in order not to mask the influence of adipose tissue, as was previously suggested (Batterham et al., 1999, De Simone et al., 2011, George et al., 2009).

Finally, with regards to the impact of obesity on LV morphology, our study shows that obesity is associated with LV concentric remodelling and hypertrophy. This has been previously shown by several studies (Gutin et al., 1998, Peterson et al., 2004, Wong et al., 2004, Woodiwiss et al., 2008) and is in contrast with the classic predominant notion that obesity is rather associated with LV eccentric hypertrophy (Nakajima et al., 1985, Smith HL,

1933). Our results suggest that visceral adiposity is the key mediator of this concentric morphology as both WC and EFT, which is the visceral fat depot of the heart, both strongly correlated with RWT. In fact, EFT displayed the strongest correlations with all the measures of LV size and morphology. Hence, as suggested by (Iacobellis et al., 2004) EFT is a better surrogate marker for visceral adiposity than WC. Several mechanisms have been proposed for LV hypertrophy in obesity including haemodynamic changes, neurohormonal factors including insulin, Angiotensin II, cathecholamines, oxidative stress and nitric oxide synthase (Garcia and Incerpi, 2008, Wong and Marwick, 2007b). Insulin-resistance and hyperinsulinemia, are believed to be responsible for the concentric morphology as several studies reported a strong association between markers of insulin resistance and fasting insulin levels and concentric LV morphology (Lind et al., 1995, Ohya et al., 1996, Sundstrom et al., 2000).

4.4.2 The allometric relationship between body size on LV function

Measures of LV function have not been routinely scaled to body size in cardiac research. Nevertheless, stroke volume index (SVI) and cardiac index (CI) are fairly popular and traditionally used measures of LV systolic function (Schuster et al., 2012, Vella et al., 2009). They consist of ratio-scaling SV and CO to BSA and are considered size independent measures of LV pump function. However, in a population of 970 normotensive individuals, (De Simone et al.,1997) showed that the relationship between SV and CO and body size is non-linear and that both SVI and CI underestimated LV function in overweight and obese subjects. The reported allometric exponents for CO scaled to BSA, BM and height were 0.62, 0.41 and 1.16 respectively and for SV scaled to the same variables were 0.93, 0.62 and 1.78 respectively. Our results are not very far from these values as the allometric exponents for SV scaled to BSA, BM and height we reported were 0.75, 0.34 and 0.97 respectively, though height did not reach statistical significance ($P > 0.05$). Furthermore, we report a significant correlation between SV and both BSA and BM, which is mediated by FFM, as SV did not correlate with FM. FFM was previously shown to be the strongest independent correlate of SV in the Strong Heart Study cohort (Bella et al., 1998, Collis et al., 2001) and an allometric exponent of 0.73 was previously reported by (Turley et al., 2007) for submaximal SV scaled to FFM in women, which is not far from our value (0.67). In our subjects, SV did not significantly differ between the normal-weight, overweight and obese groups, which is probably due to the small

differences in FFM between the 3 groups (48.7 ± 7.65 vs 47.8 ± 6.26 vs 52.1 ± 4.98 g) respectively. With regards to diastolic function, DCT was the only variable to show a significant correlation with FFM with an allometric exponent of 0.88, however it did not correlate with BSA or BM. This relationship is fairly weak (r = 29) and requires further confirmation in larger population samples.

To the best of our knowledge, the need to scale measures of LV myocardial velocity and deformation to body size has not been previously investigated. The interest in previous studies has rather been on whether or not these measures needed to be scaled to LV chamber size. Indeed, (Batterham et al., 2008) reported a close to linear correlation between LVL and both peak Sm and Em, suggesting that these two variables should be normalised to LVL. However, (Oxborough et al., 2009) reported no relationship between LV dimensions and both global LV strain and strain rate ruling out the need to normalise measures of myocardial deformation to chamber size. Our results show that myocardial velocity and strain are not influenced by overall body size or FFM. There is no need to normalise for body size prior to comparison between groups in order to explore the influence of obesity on these measures. This is not surprising given that myocardial strain is a size-independent variable as it represents the magnitude of change in length relative to the original length.

4.4.3 Impact of excess body fat on LV function

Our results indicate that, in healthy overweight and mildly obese women, excess adipose tissue is associated with a reduction in both systolic and diastolic function, the latter being more pronounced than the former.

Indeed, standard echocardiographic and tissue Doppler-derived measures of systolic function including SV, CO, EF and peak Sm were preserved in overweight and obese women. A significant reduction in longitudinal strain was observed in the obese group compared to overweight and lean counterparts. This has previously been reported by several studies (Di Salvo et al., 2006, Kuznetsova et al., 2008, Tumuklu et al., 2007, Wong et al., 2004). Log-linear correlation analysis showed a significant inverse correlation between LongS and FM, WC and EFT. There was no difference between the 3 groups in SRs in all three directions or circumferential and radial S. Interestingly, we show that LongS inversely correlated with EFT more than WC (r = -0.33 vs -0.29 respectively), and in addition, Long SRs and CircS also displayed a significant negative correlation with EFT, though

this was not the case with FM or WC. This suggests an independent negative impact of excess EFT on LV systolic strain rate, possibly indicating a mechanical influence rather than an influence of general increase in body fat. EFT was previously shown to be related to subclinical dysfunction in right ventricular strain and strain rate in patients with metabolic syndrome (Gokdeniz et al., 2014). To the best of our knowledge, this is the first reported independent association between EFT and reduced LV deformation in healthy overweight/obese females.

As for diastolic function, changes were more pronounced. A reduction in mitral annular IVRT was detected in the obese group in addition to a reversal in the ratio of early-to-late diastolic filling velocities, myocardial velocities and longitudinal SR. It was observed that the reversal in the early-to-late ratio of diastolic function was a result of increased late diastolic phase with little or no change in the early phase. This pattern was previously reported in healthy overweight/obese subjects (Di Bello et al., 2006, Koopman et al., 2012, Orhan et al., 2010, Wierzbowska-Drabik et al., 2013) and possibly reflects a very early sign of LV diastolic dysfunction since the increase in the late phase, which indicates increased left atrial contraction and/or increased LV compliance, could be compensatory to a subtle reduction in early myocardial diastolic relaxation. We also reported a paradoxical increase in CircSRe and RadSRe, possibly compensatory to the reduction in longitudinal diastolic deformation. Log-linear correlation confirmed the significant association between excess adiposity including FM, WC and EFT and LV diastolic dysfunction represented in LV diastolic filling velocities, myocardial velocity and deformation. Finally, measures of preload and afterload were all preserved in our subjects including LV end-diastolic volume, left atrial diameter and volume, E/Em ratio and LV SWS, indicating that systolic and diastolic functional changes were not a reflection of changes in pre-load or after-load. Several mechanisms have been proposed to explain the adverse LV systolic and diastolic functional changes associated with obesity. The most well-recognised mechanism of LV dysfunction is the haemodynamic mechanism (Alpert, 2001, Wong et al., 2004). The high metabolic demands associated with obesity result in a high intravascular blood volume. This results in increased preload with subsequent increased stroke volume by the Frank-Starling mechanism. LV chamber dilatation and stretching of the walls of the LV with the increased wall stress, induce LV remodelling and hypertrophy to reduce wall stress. This pathological hypertrophy results in myocardial fibrosis and reduced LV compliance leading to diastolic function. Eventually, afterload also develops

and LV systolic dysfunction occurs. However, recent evidence suggest that other mechanisms play important roles in LV dysfunction including insulin-resistance induced metabolic changes in glucose vs fatty acid utilisation, myocardial fatty infiltration and steatosis, pro-inflammatory cytokine release and reactive oxygen species, leptin-insensitivity and reduced adiponectin expression, all of which result in contractile dysfunction and subsequent systolic and diastolic failure.

4.4.4 Conclusions

This study has several outcomes: (1) It confirms the strong impact of body size and composition on LV size and the importance of normalising LV size variables to body size, particularly FFM, using allometric scaling before the comparison between subjects is to be carried out. Furthermore, If the impact of excess body fat is to be studied, especially in mild obesity, scaling for BSA, even using allometric procedures, may underestimate LV size and mask the influence of adipose tissue. Therefore FFM should be used instead using sample-specific allometric power exponents. (2) This study highlights the importance of novel TDI and 2DST echocardiographic techniques and their higher sensitivity in detecting subclinical and subtle systolic and diastolic dysfunction in mild obesity compared to standard echocardiography. Indeed, we show that, in healthy overweight and obese women, visceral adiposity is associated with concentric LV morphology, decreased LV longS, Em and LongSRe with compensatory increase in CircSRe and ʀadSRe despite normal standard echocardiographic measures of systolic and diastolic function. (3) Epicardial fat thickness is strongly associated with obesity-mediated LV structural and functional changes and appears to have an independent negative mechanical impact on LV systolic deformation, not mediated through general adiposity.

4.4.5 Study limitations

This study included women only and does not take into account other physiologically relevant factors such as race or age. Furthermore, the number of participants is relatively small, which would have affected the strength of our observations. Finally, this is a cross-sectional observational study performed at one point in time and hence does not give information on cause and effect. Bigger-sized longitudinal studies, supported by cellular and molecular techniques are needed in order to determine explanatory mechanisms of the observed findings, follow their change over time at both

the population and individual levels and increase the statistical strength of the observations.

Chapter 5 The assessment of left ventricular response to heavy-intensity exercise in obese women

5.1 Introduction

Overweight and obesity are important independent risk factors for the development of heart failure in women (Dagenais et al., 2005). They mediate subtle LV morphological and functional changes in otherwise healthy individuals, that can remain silent for years and undetectable by standard echocardiography. In the previous chapter excess body fat, particularly visceral adipose tissue, was associated with concentric LV remodelling and reduced systolic and diastolic myocardial deformation despite normal EF, SV and CO in healthy normotensive overweight/obese women. Weight loss can be a challenging task for obese women, and its maintenance remains extremely difficult. Furthermore, the worldwide prevalence of obesity is on the rise (Rennie and Jebb, 2005). Recent evidence suggest that exercise alone can improve and restore cardiac function in obese individuals without the need for dietary modification and weight loss (Ingul et al., 2010, Schuster et al., 2012). Indeed, Ingul et al. showed that, in obese adolescents, LV systolic and diastolic function both at rest and during exercise, improved to levels comparable to non-obese controls after 3 months of aerobic training, without any accompanying weight loss (Ingul et al., 2010). Despite the large body of evidence on the LV structural and functional adaptations to short and long periods of aerobic exercise training in healthy mild-moderately obese individuals (Baynard et al., 2008, Eriksson et al., 2010, Humphries et al., 2002, Ingul et al., 2010, Millen et al., 2014, Mitchell et al., 2002, Schrauwen-Hinderling et al., 2010, Schuster et al., 2009, Sijie et al., 2012, Stewart et al., 2006, Vogelsang et al., 2008, Weiner and Baggish, 2012), very little is known about LV systolic and diastolic functional changes during acute exercise in this population, particularly women. Older studies tended to assess morbidly obese subjects (Alexander and Peterson, 1972, Alpert et al., 1989, Ferraro et al., 1996, Salvadori et al., 1999) and to date, most studies have predominantly focused on CO, SV and/or EF during exercise (Alpert et al., 1989, Ferraro et al., 1996, Licata et al., 1992, Rowland et al., 2003, Sasso et al., 2005, Vella et al., 2009). These measures are strongly influenced by changes in preload and afterload and are not sensitive enough to detect subtle changes in

myocardial contractility during exercise. Only two studies have assessed LV myocardial velocity during exercise in obese children (Ingul et al., 2010, Schuster et al., 2012) and of these two studies, only one study assessed longitudinal deformation (Ingul et al 2010). Schuster demonstrated that moderately obese children, despite having similar peak Sm to lean controls at rest and throughout incremental exercise, they reached significantly lower levels at submaximal and maximal exercise. This was not the case for overweight children that displayed similar LV systolic function to lean controls both at rest and during all exercise intensities. This may indicate that LV systolic function is preserved in mild degrees of obesity and that as the degree of obesity increases, subtle reductions in LV systolic function may occur (Schuster et al., 2012). Ingul reported lower LV systolic and diastolic myocardial velocity and deformation both at rest and during cycling at a workload of 100 W in obese adolescents compared to lean counterparts. However, this technique of using an absolute rather than relative workload does not account for individual differences in cardio-pulmonary fitness and hence may result in discrepancies between subjects. Furthermore, this study did not assess the amount of exercise-induced change in LV function between both groups (Ingul et al., 2010).

LV function during exercise has been predominantly assessed during incremental exercise test until exhaustion (Licata et al., 1992, Rowland et al., 2003, Schuster et al., 2012) or during steady cycling at fixed work rates of 40-50 W, 70-75 W and/or 100 W (Salvadori et al., 1999, Vella et al., 2009, Ingul et al., 2010). This does not accurately normalise the exercise intensity between subjects as it does not account for individual differences in cardiorespiratory fitness. Participants exercising at these fixed work rates may be at different exercise intensities above or below their lactate threshold depending on their level of cardiorespiratory fitness. Thus, the physiological stimulus for LV response to exercise may vary between participants which may lead to disparity in results between studies or between participants of the same study.

To date, the assessment of LV function during acute heavy-intensity exercise, determined based on individual lactate thresholds, in healthy overweight/obese women has not been studied. Furthermore, no information is available in the literature on LV systolic and diastolic function during recovery from acute heavy-intensity exercise in healthy overweight/obese women or indeed in obese subjects in general.

Therefore, the aims of this chapter were to compare between healthy overweight/obese and non-obese women with regards to LV systolic and diastolic function during, and after 5 minutes of recovery from, heavy-intensity exercise using standard and novel echocardiographic techniques. This will potentially allow the identification of the presence or absence of subtle LV systolic and/or diastolic dysfunction in overweight/obese women not detected at rest and only revealed under the additional exercise-induced stress. Furthermore, it will allow the potential identification of beneficial exercise-induced alterations in LV function, which would help expand our understanding of LV adaptation to aerobic exercise training. Finally, it will allow the potential identification of differences between overweight/obese and non-obese women in LV response to exercise secondary to excess body fat. It was hypothesised that healthy overweight/mildly obese women would display subtle exercise-induced reduction in LV function not detected at rest and would manifest greater benefit than non-obese women from heavy-intensity exercise on LV function.

5.2 Methods

5.2.1 Participants

Sixteen healthy women (age 33.4 ± 3.9 years) were recruited for the study through local poster advertisements across the University of Leeds campus. All volunteers confirmed being healthy and free of known cardiovascular disease and were not on any form of prescribed medication. Exclusion criteria other than specified in the general methods included involvement in regular and/or heavy physical exercise more than twice weekly. A 12-lead ECG was carried out at rest prior to testing and throughout the cardiopulmonary exercise test to rule out ECG abnormalities.

5.2.2 Experimental protocol

Participants were invited to attend the University of Leeds exercise physiology laboratory on two occasions. On the first visit, participants were first given a chance to familiarise themselves with the equipment and ask questions. Then, after recording their anthropometric measurements, participants completed a cardiopulmonary fitness test for the assessment of VO_{2max} and LT, in order to be used for the calculation of the work-rates to be used for the subsequent exercise sessions. The second visit was at least one week after the first one and consisted of a 10-minute heavy-intensity

exercise on a semi-supine bicycle ergometer (Lode BV Medical Technology, Groningen, Netherlands). The echocardiographic assessment of LV function was carried out at rest, 8 min after the start of cycling and 5 min after the end of the exercise session (Figure 5.1). The control factors for the two sessions are detailed in the general methods chapter.

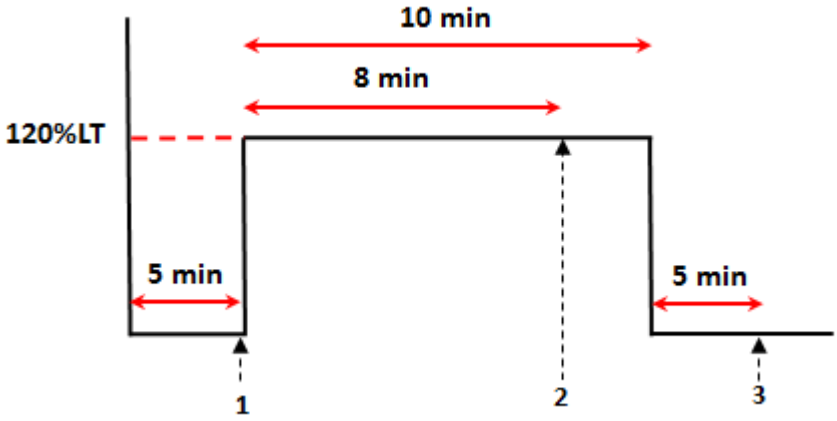

Figure 5. 1 Schematic representation of the heavy-intensity exercise session. Echocardiographic imaging was carried out at 3 time points, (1) after 5 min of rest, (2) after 8 min of heavy-intensity exercise in the form of semi-supine cycling at 120%LY and (3) after 5 min recovery.

5.2.3 Measured variables

5.2.3.1 Anthropometric variables

Anthropometric measurements included body mass (BM), height (HT), waist circumference (WC), hip circumference (HC) and waist to hip ratio (W:H ratio). Body mass index (BMI) and body surface area (BSA) were calculated as explained in the general methods chapter.

5.2.3.2 Echocardiographic variables

Echocardiographic techniques are explained in details in the General Methods chapter (Chapter 3, section 3.4). Echocardiography was completed at rest, after 8 min of the start of the exercise session and 5 min after the end of the session and included standard 2D, PWD, TDI and 2DST echocardiography. Standard 2D measurements included IVSTd, PWTd, LVIDd, LVM, RWT, LAD, EDV, ESV, SV, EF and LAV. PWD echocardiographic variables included E, A, E:A, IVRT and DCT. TDI echocardiographic variables included Em, Am, Em:Am and E/Em. Finally, 2DST echocardiographic variables included LongS, LongSRs, LongSRe, LongSRa, LongSRe/a, CircS, CircSRs, CircSRe, CircSRa, CircSRe/a, RadS, RadSRs, RadSRe, RadSRa, RadSRe/a and LVTor.

5.2.3.3 Cardiopulmonary fitness

An incremental ramp test was performed on a semi-supine cycle ergometer at 12 W/min to determine maximal oxygen uptake (VO_{2peak}) and WR_{peak}. This was followed by a step exercise at 105% WR_{peak} to determine a second VO_{2peak}, and the average of both were used as VO_{2max} as explained in the general methods (Chapter 3, section 3.5). Lactate threshold (LT) and its corresponding WR (WR_{LT}) were then determined for the calculation of 120% WR_{LT} to be exercised at in the subsequent exercise session.

5.2.4 Exercise session protocol

All participants refrained from vigorous exercise for 24 hours and avoided alcohol and caffeine for 4 hours prior to exercise session. Participants completed a 10-min heavy-intensity exercise session on a semi supine cycle ergometer. The exercise session consisted of cycling in the semi-supine position at 120% WR_{LT}, which falls in the heavy intensity domain (Rossiter, 2011). Prior to commencement of the session, participants were seated on the semi-supine cycle ergometer for a 5-min rest period followed by a 2-min warm-up period of unloaded cycling at 20 W. During the rest period, baseline echocardiographic assessment of LV function was carried out. After 8 min of cycling at 120% WR_{LT}, the cycle ergometer was tilted slightly to the left, a second echocardiographic assessment of LV function was performed during exercise and then the cycle ergometer was tilted back to its original position. Participants were instructed to maintain a cadence of > 60 rpm throughout the session which was stopped after 10 min of cycling. Finally, a third echocardiographic assessment of LV function was carried out after 5 min of recovery. A schematic representation of the exercise session protocol is presented in Figure 5.1.

5.2.5 Statistical analysis

Data were checked for normality of distribution using a Kolmogorov-Smirnov test. Both groups' resting anthropometric, blood pressure, cardiorespiratory and echocardiographic parameters were compared using independent t-tests. The effect of exercise and recovery were analysed using a mixed mode ANOVA with repeated measures for time (rest vs. exercise vs. recovery) as the within subjects factor and group (obese vs. non-obese) as the between-subjects factor. At rest, HR, IVRT and Em/Am were significantly different between the two groups ($P < 0.05$), therefore resting values of these variables were added as covariate to the ANOVA. Post-hoc analysis was carried out using paired t-tests in the presence of significant

time by group interaction to identify which variables changed significantly. Student's independent t-tests were performed to compare between both groups' percentage change from rest to exercise.

5.3 Results

5.3.1 Participant and exercise session characteristics

The anthropometric, BP and cardio-respiratory fitness characteristics of the obese and non-obese groups are displayed in Table 5.1. The total number of participants was 16, consisting of 8 obese and 8 non-obese females. The obese group had a significantly higher average weight, BMI, BSA, WC and W:H ratio than the non-obese group ($P < 0.05$). Both groups had similar BP readings. With regards to cardio-respiratory fitness, absolute VO_{2max}, LT, LT% and WR_{LT} did not differ between groups ($P > 0.05$) However the obese group had a significantly lower relative VO_{2max} ($P < 0.05$) and a trend for a lower average $WR_{120\%LT}$ than the non-obese group ($P = 0.08$). All 16 participants completed the exercise sessions. Groups did not differ in LV size and morphology including LVM, LVIDd, PWT, IVSTd and RWT ($P > 0.05$).

Table 5. 1 Anthropometric, body composition, BP and cardio-respiratory fitness measurements (mean ± SD) of the obese and non-obese women

	Obese	Non-Obese
Weight (kg)	93.8 ± 11.2 *	67.3 ± 7.2
Height (m)	1.63 ± 0.17	1.71 ± 0.08
BMI (kg/m^2)	32.9 ± 3.5 *	22.9 ± 1.1
BSA (m^2)	1.99 ± 0.18 *	1.79 ± 0.14
Waist (cm)	100.6 ± 12.4 *	74.6 ± 5.1
W:H ratio	0.87 ± 0.09 *	0.77 ± 0.03
SBP (mmHg)	122.5 ± 7.1	120 ± 9.3
DBP (mmHg)	81.3 ± 2.3	79.4 ± 6.8
Absolute VO_{2max} (L/min)	2.09 ± 0.56	2.53 ± 0.83
Relative VO_{2max} (ml/kg/min)	22.6 ± 6.35 *	37.0 ± 8.04
LT (L)	1.08 ± 0.18	1.19 ± 0.31
LT (%)	53.2 ± 11.2	48.4 ± 10.2
WR_{LT} (W)	64.4 ± 8.5	77.4 ± 19.1
$WR_{120\%LT}$ (W)	75.5 ± 11.03 †	92.8 ± 23.1
LVM (g)	133.8 ± 27.2	129.9 ± 18.4
LVIDd (cm)	4.21 ± 0.51	4.51 ± 0.49
PWTd (cm)	0.94 ± 0.2	0.93 ± 0.12
IVSTd (cm)	1.01 ± 0.18	0.96 ± 0.18
RWT	0.47 ± 0.09	0.42 ± 0.07

BMI = body mass index, BSA = body surface area, W:H ratio = waist to hip ratio, SBP = systolic blood pressure, DBP = diastolic blood pressure, LT = lactate threshold, WR_{max} = work rate at VO_{2max}, $WR_{120\%LT}$ = work rate at 120% of lactate threshold. LVM = left ventricular mass, LVIDd = LV diastolic internal diameter, PWTd = diastolic posterior wall thickness, IVSTd = diastolic inter-ventricular septum thickness, RWT = relative wall thickness. * = significant difference ($P < 0.05$) between obese and non-obese groups. † = close to significant difference ($P < 0.09$) between obese and non-obese groups.

5.3.2 Haemodynamic parameters and internal dimensions

At baseline, obese participants had significantly higher resting HR compared to the non-obese group ($P < 0.05$) and a trend for a greater CO than their non-obese counterparts ($P = 0.08$). All the remaining resting haemodynamic parameters did not differ between the two groups (Table 5.2).

Table 5. 2 Left ventricular haemodynamic parameters (mean ± SD) during heavy-intensity exercise at 120%LT and at 5-min recovery in obese and non-obese women

	Obese			Non-Obese		
	Baseline	120%LT	Recovery	Baseline	120%LT	Recovery
HR (bpm)	69±7	127±12	78±6 §	59±9*	119±12	62±10*
SBP (mmHg)	123±7	166±11	126±9	120±9	150±8*	123±9
EDV (ml)	105.3±24.4	121.3±34.8	107±25	108.4±27.3	117.8±29.4	112±25.2
ESV (ml)	30.9±4.1	23.8±5.9	27.9±2.53	34±14.4	26.9±13.9	32.3±12.4
SV (ml)	73.8±22.6	97.6±31.7	79.1±24.9§	74.3±15.7	90.9±17.2	79.6±15.2§
EF (%)	69.5±6.3	79.8±5.23	72.8±6.5§	69.4±5.9	78.6±6.19	72±5.4§
CO (L)	5.12±1.65	12.25±3.78	6.12±1.8§	4.32±0.52†	10.69±1.49	4.86±0.7†§
LAV (ml)	38.5±7.6	45.7±13.7	36.8±10	38.6±11.2	46.4±13.2	36.6±9.9

HR = heart rate, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, LAV = left atrial volume, EF = ejection fraction, COP = cardiac output. * indicates significant difference from the obese group at the same time point ($P < 0.05$). † indicates a trend for difference from the obese group at the same time point. § indicates significant difference from baseline (time effect $P < 0.05$). All variables at 120%LT were significantly higher than baseline (Time effect $P < 0.05$)

During heavy-intensity exercise, both groups showed a significant increase in all haemodynamic parameters (Time effect, $P < 0.05$; Table 5.3). Heart rate and SV increased by ~90% and ~27% respectively resulting in a ~140% increase in CO. The exercise-induced increase in SV (~30%) was driven by a ~22% decrease in ESV and a ~12% increase in EDV. Left atrial volume increased during exercise by ~16%. Finally, EF increased by ~ 14% during exercise. A significant time by group interaction ($P < 0.05$) was observed for SBP with post-hoc analysis revealing a significantly higher SBP during exercise in the obese compared to the non-obese group (26% vs 20% respectively; Figure 5.2). No other time by group interactions were observed.

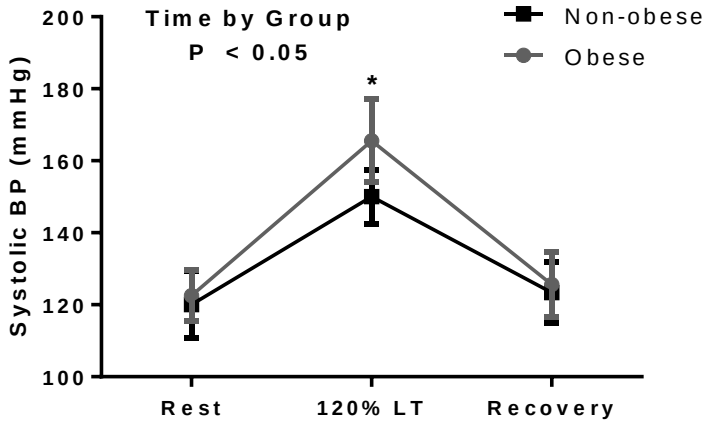

Figure 5. 2 Heavy-intensity exercise-induced increase in systolic blood pressure (SBP) in obese and non-obese women. * indicates significant difference between the two groups (P < 0.05). Time by group interaction, P < 0.05

At 5-min recovery, SBP, EDV, ESV and LAV returned to resting levels in both groups whereas HR, SV, CO and EF were significantly higher than at rest (Time effect; P < 0.05). A significant time by group interaction was observed for HR with post-hoc analysis revealing that only the obese group had a significantly higher HR at 5-min recovery than baseline (P < 0.05) whereas the non-obese group's HR at recovery did not differ from rest as shown in Figure 5.3. This time by group interaction remained significant even after correcting for baseline HR. No other time by group interactions were observed.

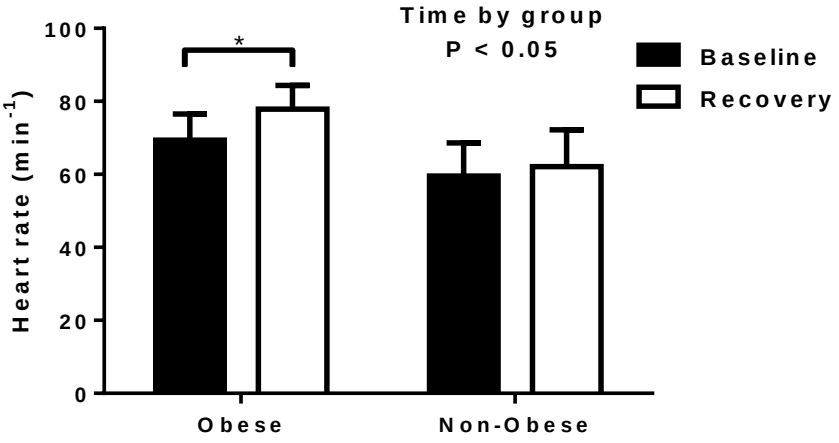

Figure 5. 3 Heart rate at baseline and after 5 min recovery following 10 min of heavy-intensity exercise in obese and non-obese women. * indicate significant difference between baseline and recovery (P < 0.05). Time by group interaction, P < 0.05.

5.3.3 Left ventricular mitral inflow and tissue Doppler parameters

At baseline, obese participants displayed significantly longer IVRT than their non-obese counterparts ($P < 0.05$). Also, obese subjects showed a trend for higher Am velocity ($P = 0.08$) and significantly lower Em/Am ratio than non-obese participants ($P < 0.05$). No other differences were detected between the 2 groups at baseline (Table 5.3).

Table 5. 3 Changes in mitral inflow and tissue Doppler velocities (mean ± SD) during exercise at 120%LT and after 5-min recovery in obese and non-obese women

	Obese			Non-Obese		
	Baseline	120%LT	Recovery	Baseline	120%LT	Recovery
E (ms)	0.94±0.18	1.44±0.27	0.9±0.09	0.93±0.1	1.54±0.33	0.97±0.13
A (ms)	0.53±0.14	N/A	0.52±0.06	0.52±0.15	N/A	0.44±0.14
E/A	1.93±0.8	N/A	1.75±0.27	1.96±0.61	N/A	2.28±0.44
DCT (ms)	181.6±40.4	83.7±25.2	140.7±59.4‡	183.1±36.3	109.7±31.8†	162±33.7‡
IVRT (ms)	67.9±12.8	36.6±16.2	66.1±19.7	85.3±16.1*	36.5±11.9	87.3±19.8*
Sm	7.18±0.5	10±0.93	7±1.6	6.84±1.74	10.1±2.22	6.7±1.9
Em	10.45±1.66	14.55±1.87	11.39±0.99	11.32±2.96	12.76±3.17	11.25±1.87
Am	6.08±0.77	N/A	6.25±2.34	4.88±1.72†	N/A	4.47±1.72
Em/Am	1.75±0.39	N/A	2.12±0.94§	2.39±0.36*	N/A	2.72±0.65§
E/Em	9.12±2.45	10.14±2.97	7.93±2.63	8.85±2.8	11.08±2.57	8.83±1.81

E = early diastolic mitral inflow velocity, A = late diastolic mitral inflow velocity, DCT = deceleration time, IVRT = isovolumic relaxation time, Sm = systolic myocardial velocity, Em = early diastolic myocardial velocity, Am = late diastolic myocardial velocity. * indicates significant difference from the obese group at the same time point ($P < 0.05$). † indicates a trend for difference from the obese group at the same time point. § indicates significant difference from baseline (time effect $P < 0.05$). ‡ indicates close to significant difference from baseline (time effect $P < 0.09$). All variables at 120%LT were significantly higher than baseline (Time effect $P < 0.05$)

As shown in Table 5.3, all indices of mitral inflow and tissue Doppler velocities changed significantly during heavy-intensity exercise in both groups, with a ~38% increase in E velocity, a ~48% decrease in DCT, a ~54% decrease in IVRT, a ~40% increase in Sm, a ~27% increase in Em and a ~20% increase in E/Em (Time effect; $P < 0.05$). A significant time by group interaction was detected for IVRT ($P < 0.05$) but disappeared after correcting for baseline differences between both groups. No difference was detected between both groups' exercise-delta IVRT ($P > 0.05$). During heavy-intensity exercise, a trend for a greater reduction in DCT was observed in the obese compared to the non-obese group (exercise-delta DCT = ~58% vs 40% respectively, $P = 0.09$, time by group interaction $P >$

0.05; Figure 5.4). Furthermore, both BMI and WC displayed significant negative correlations with exercise-delta DCT (r = -0.53 and -0.56 respectively, P < 0.05; Figure 5.5a and 5.5b). A significant time by group interaction was observed for Em and post-hoc analysis revealed that the exercise-induced increase in Em in the obese group was significantly greater than the lean counterparts (41% vs. 14% respectively, time by group interaction P < 0.05; Figure 5.6). Additionally, BMI and WC showed significant positive correlations with exercise delta Em (r = 0.61 and r = 0.63 respectively, P < 0.05; Figure 5.7a and 5.7b).

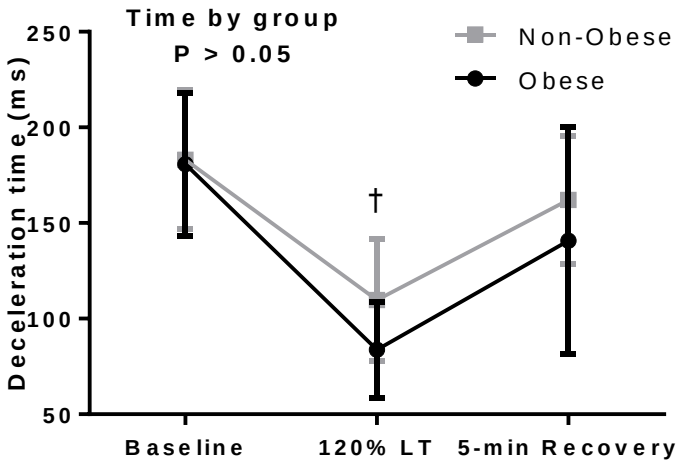

Figure 5. 4 Heavy-intensity exercise-induced decrease in early diastolic filling deceleration time (DCT) in obese and non-obese women. † indicates a close to significant difference between the two groups (P = 0.09). Time by group interaction, P > 0.05.

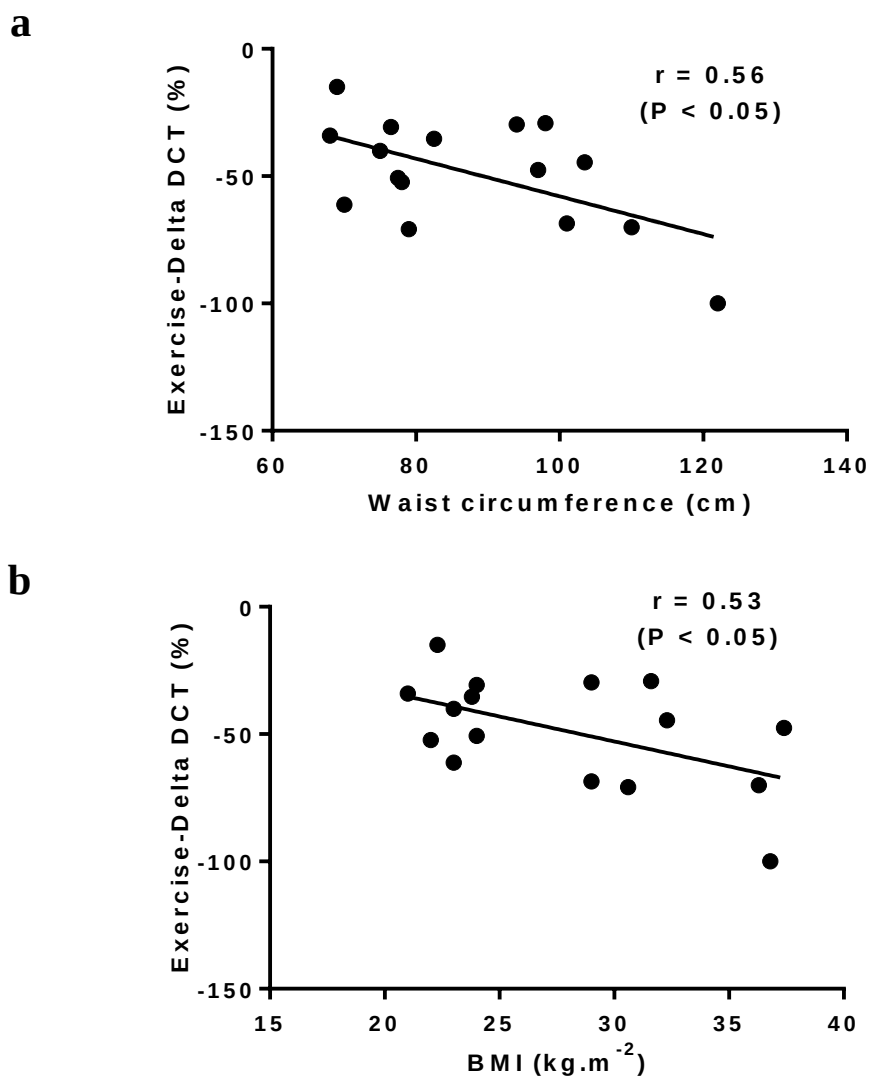

Figure 5. 5 Relationship between high-intensity exercise-induced decrease in deceleration time (DCT) and obesity in women. (a) a significant negative correlation was observed between exercise-induced decrease in DCT (delta-exercise DCT) and (a) waist circumference ($r = 0.56$, $P < 0.05$) and (b) BMI ($r = 0.53$, $P < 0.05$).

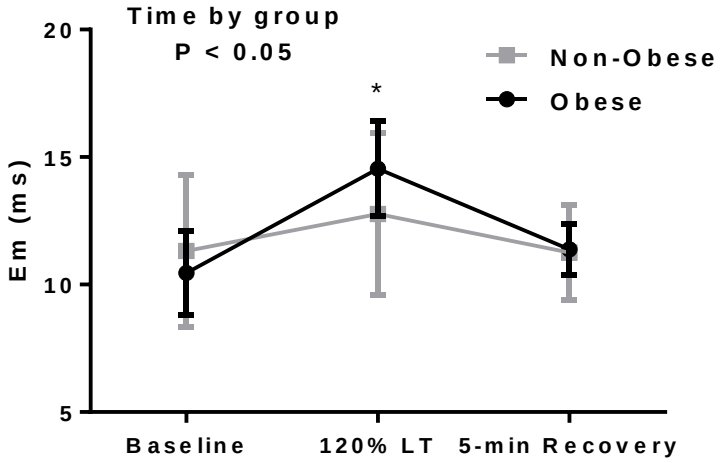

Figure 5. 6 Heavy-intensity exercise-induced increase in early diastolic myocardial velocity (Em) in obese and non-obese women. * indicates a significant difference between the two groups (P < 0.05). Time by group interaction, P < 0.05.

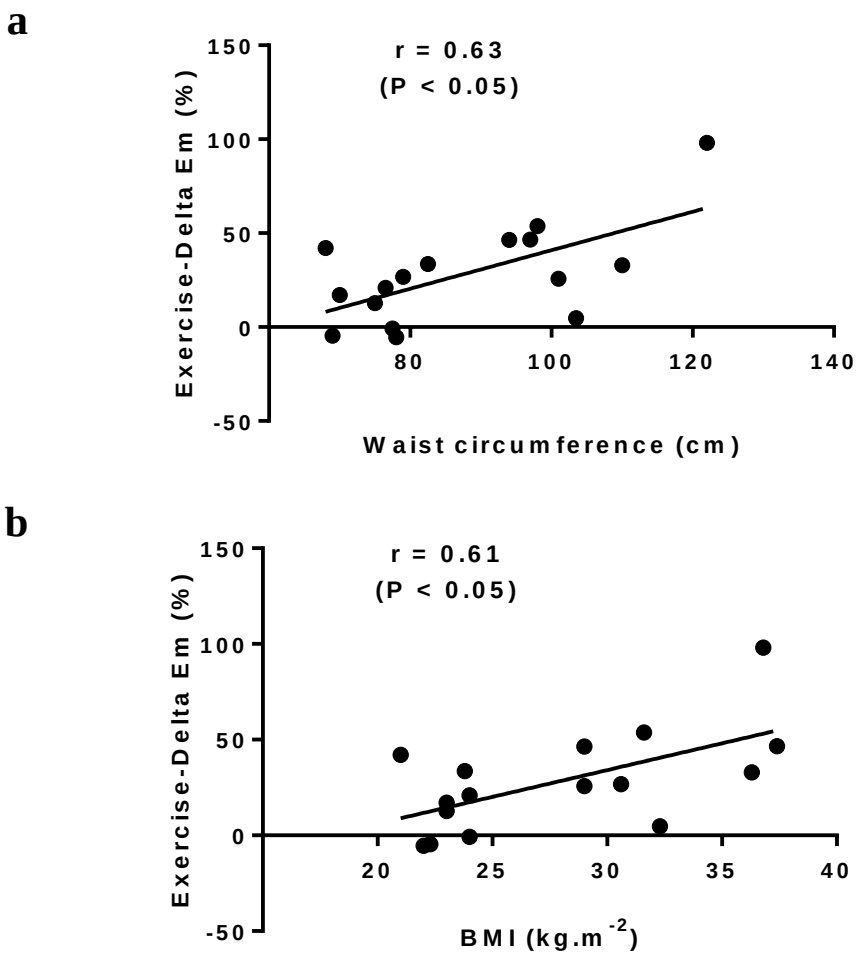

Figure 5. 7 Relationship between high-intensity exercise-induced increase in Em and obesity in women. (a) a significant positive correlation was observed between exercise-induced increase in Em (delta-exercise Em) and (a) waist circumference (r = 0.63, P < 0.05) and (b) BMI (r = 0.61, P < 0.05).

At 5-min recovery both groups' E, A, E/A, IVRT, Sm, Em, Am and E/Em returned to their baseline levels (Time effect, P > 0.05) whereas Em/Am was higher and DCT was lower than baseline in both groups (Time effect; P < 0.05 and 0.08 respectively, time by group interaction P > 0.05 for both). A trend for time by group interaction was observed for E/A (time by group interaction, P = 0.09) with post-hoc analysis revealing a E/A at 5-min recovery higher than rest in the non-obese group with strong effect size(P > 0.05, d = 0.6) whereas it was lower than rest in the obese group with mild effect size (P > 0.05, d = 0.3; Figure 5.8).

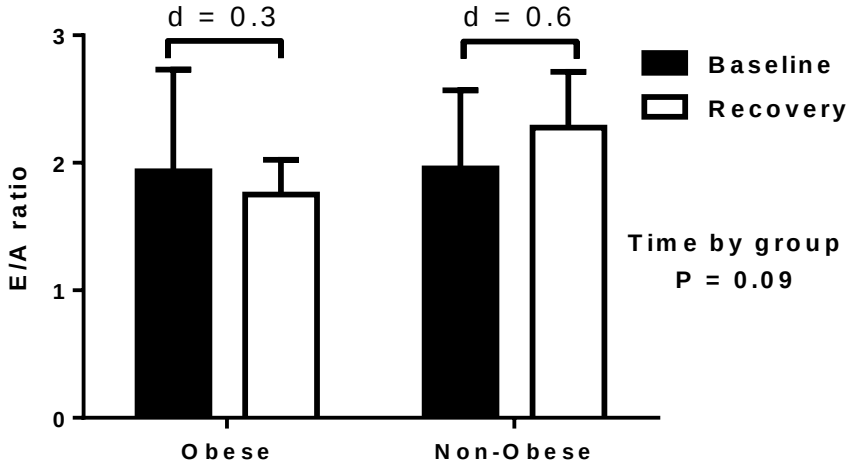

Figure 5. 8 E/A ratio at baseline and after 5 min recovery following 10 min of heavy-intensity exercise in obese and non-obese women. Obese women had a lower E/A ratio at 5 min recovery than rest whereas the opposite was observed in non-obese women (time by group interaction, P < 0.05). d indicates Cohen's effect size.

5.3.4 Left ventricular myocardial deformation and torsion

Baseline measures of myocardial deformation and torsion were similar in both groups (P > 0.05). Table 5.4 displays the changes in myocardial deformation and torsion during heavy-intensity exercise and 5-min recovery in obese and non-obese subjects.

During heavy-intensity exercise, all measures of myocardial deformation and torsion increased significantly in all 3 planes of motion (Time effect, P < 0.05). Exercise-induced increase in LV strain was ~20% in the longitudinal, ~29% in the circumferential and ~39% in the radial directions with no difference between groups (time by group interaction, P > 0.05). The exercise-induced increase in SRs was ~77% in the longitudinal, ~85% in the circumferential and ~50% in the radial directions. No time by group

interactions were detected for LongSRs or CircSRs, however a trend was detected for RadSRs with post-hoc analysis showing a significantly higher exercise-induced increase in RadSRs in the obese group (~80%, $P < 0.05$) compared to the non-obese group (~19%, $P = 0.07$; Figure 5.9a). Furthermore, a close to significant direct correlation was observed between exercise-induced increase in RadSRs and BMI ($r = 0.48$, $P = 0.08$; Figure 5.9b) During heavy-intensity exercise, SRe increased by ~42% in the longitudinal, ~65% in the circumferential and ~96% in the radial directions with no differences between groups (Time effect, $P < 0.05$; Time by group interaction, $P > 0.05$). Finally, LVTor only increased by ~4% during heavy-intensity with no difference between groups (Time effect, $P < 0.05$; Time by group interaction, $P > 0.05$).

Table 5. 4 Changes in LV myocardial deformation and torsion (mean ± SD) during heavy-intensity exercise (120% LT) and after 5-min recovery in obese and non-obese women

	Obese			Non-Obese		
	Baseline	120%LT	Recovery	Baseline	120%LT	Recovery
Strain (%)						
LongS	16.8±2.69	19.6±2.1	15.7±2.32	18.3±3.22	22.34±5.33	17.9±2.67
CircS	15.8±2.87	19.7±3.36	17±3.46	17.9±3.4	22.8±4.01	16.7±3.02
RadS	15.1±2.41	20.9±7.42	15.2±5.48	16.7±2.9	22.3±10.7	14.5±3.18
SRs (ms)						
LongSRs	0.88±0.25	1.44±0.26	0.88±0.23	0.96±0.23	1.75±0.54	0.93±0.19
CircSRs	0.97±0.27	1.8±0.37	1.1±0.24	1.05±0.28	1.8±0.5	1.02±0.17
RadSRs	1.33±0.3	2.33±0.46	1.6±0.47	1.47±0.42	1.99±0.66	1.1±0.42*
SRe (ms)						
LongSRe	1.4±0.3	1.89±0.46	1.22±0.23	1.71±0.42	2.31±0.37†	1.72±0.41*
CircSRe	1.42±0.45	2.13±0.76	1.59±0.18	1.53±0.5	2.25±0.86	1.27±0.3*
RadSRe	1.25±0.58	2.36±0.71	1.6±0.58	1.18±0.23	2.41±1.03	1.42±0.45
SRa (ms)						
LongSRa	0.6±0.14	N/A	0.6±0.2	0.54±0.19	N/A	0.47±0.17
CircSRa	0.4±0.26	N/A	0.56±0.34	0.33±0.22	N/A	0.35±0.17
RadSRa	0.71±0.19	N/A	0.79±0.21	0.59±0.32	N/A	0.42±0.12*
SRe/a						
LongSRe/a	2.51±0.88	N/A	2.27±1.0	3.28±0.57†	N/A	3.97±1.22*
CircSRe/a	5.4±3.95	N/A	4.03±2.74	5.87±3.27	N/A	4.28±1.62
RadSRe/a	1.58±0.54	N/A	2.01±0.72	2.47±1.21†	N/A	3.17±0.89*
Torsion	10.2±2.55	14.2±3.03	10.3±3.12	8.9±4.38	12.4±5.03	8.5±4.38

SRs= systolic strain rate, SRe = early diastolic strain rate, SRa = late diastolic strain rate. * indicates significant difference from baseline ($P < 0.05$). All variables at 120%LT were significantly different from baseline (time effect, $P < 0.05$).

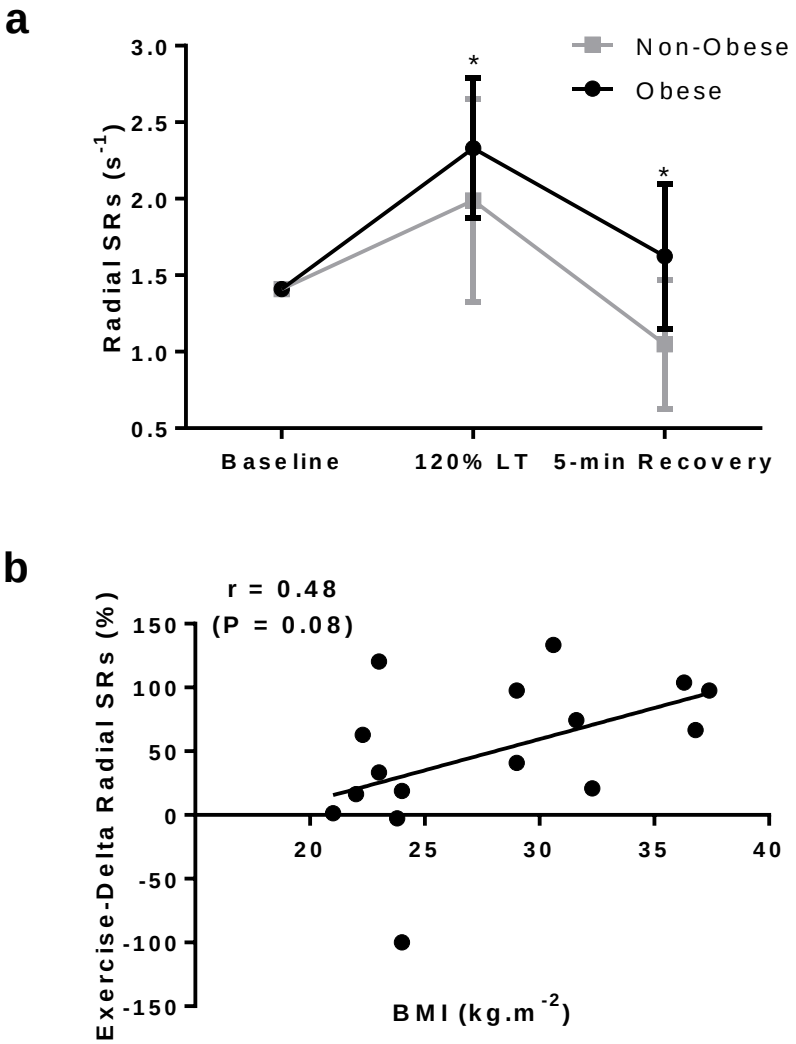

Figure 5. 9 Impact of heavy-intensity exercise on radial systolic strain rate (RadSRs) in obese and non-obese women. (a) Obese women had a significantly greater increase in RadSRs at 120%LT and 5-min recovery compared to non-obese women (time by group interaction, $P < 0.05$). (b) Relationship between heavy-intensity exercise-induced increase in RadSRs and obesity, a significant positive correlation was observed between exercise-induced increase in RadSRs (delta-exercise RadSRs) and BMI ($r = 0.48$, $P = 0.08$). * indicates a significant difference between the two groups ($P < 0.05$)

At 5-min recovery, LV strain, strain rate and torsion returned to their baseline levels (Time effect, $P > 0.05$; Table 5.4). A significant time by group interaction was observed for RadSRs with post-hoc analysis showing significantly lower RadSRs at recovery than rest in the non-obese group,

whereas the obese group's RadSRs returned to resting level (Figure 5.9a). A trend for time by group interaction was observed for RadSRa with post-hoc analysis showing a higher RadSRa at 5-min recovery than rest in the non-obese group (P > 0.05, cohen's d = 0.7) whereas it was lower than rest in the obese group (P > 0.05, cohen's d = 0.4; time by group interaction, P = 0.06; Figure 5.10a). Despite a lack of significant time by group interaction for RadSRe/a (P > 0.05), a higher value than rest was noticed in the non-obese group at 5-min recovery with strong effect size (P > 0.05, d = 0.6), however this was not observed in the obese group (Figure 5.10b).

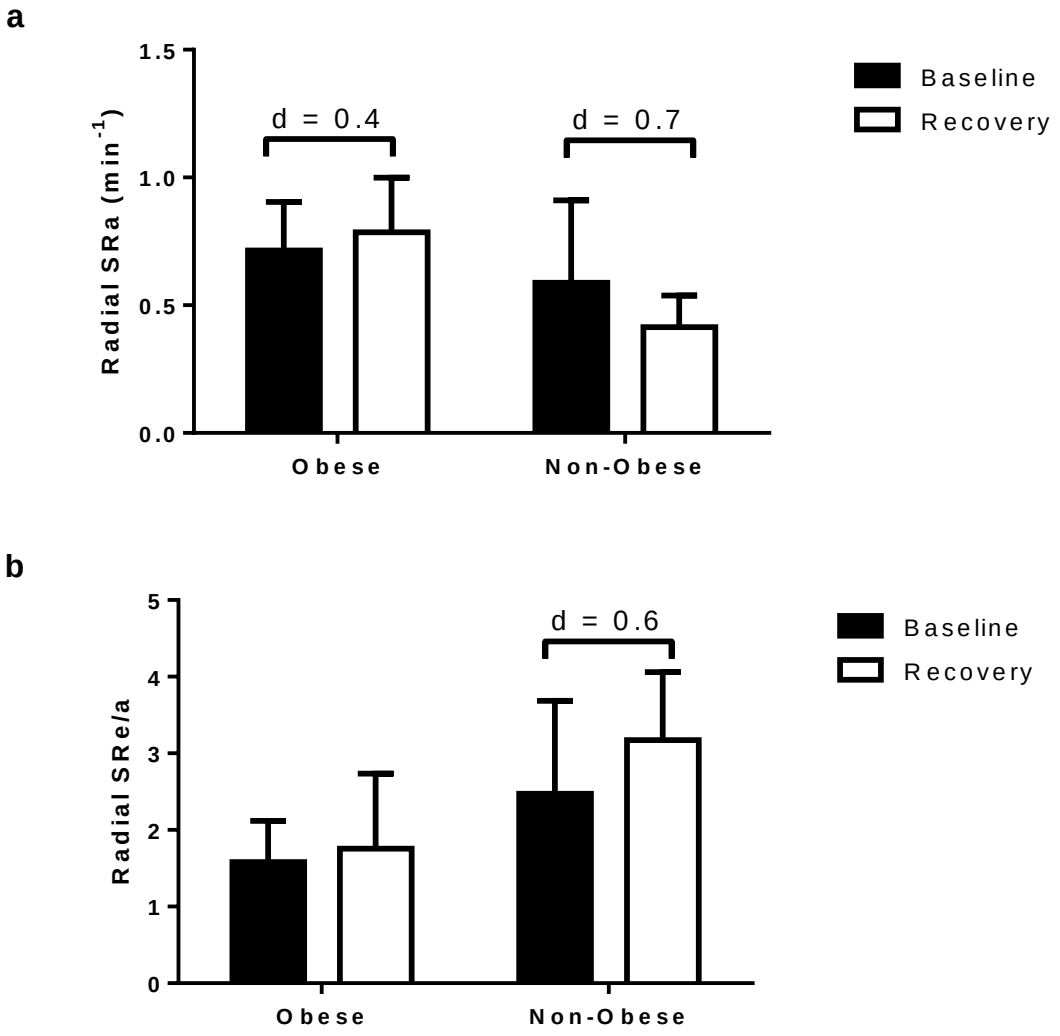

Figure 5. 10 Radial diastolic strain rate after 5-min recovery following heavy intensity exercise in obese and non-obese women. (a) At 5-min recovery, RadSRa was lower than rest in non-obese woman whereas it was higher than rest in obese women. (b) RadSRe/a was higher than rest in the non-obese women with no change in the obese women. d indicates Cohen's effect size.

Despite the absence of a significant time by group interaction for LongSRe, LongSRa and LongSRe/a (P > 0.05), it was observed that, at 5-min recovery, LongSRe was lower than baseline in the obese group (P > 0.05, cohen's d = 0.7; Figure 5.11), LongSRa was higher than baseline in the non-obese group (P = 0.08; Figure 5.12) and LongSRe/a was higher than baseline in the non-obese group (P < 0.05; Figure 5.13).

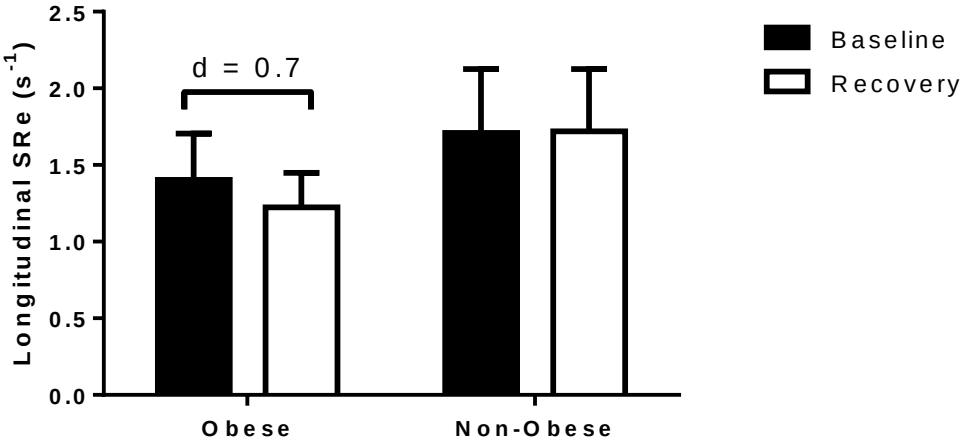

Figure 5. 11 Longitudinal SRe after 5-min recovery following heavy intensity exercise in obese and non-obese women. At 5-min recovery, LongSRe was lower than rest in the obese group with no change in the non-obese group. Time by group interaction, P > 0.05. d indicates Cohen's effect size.

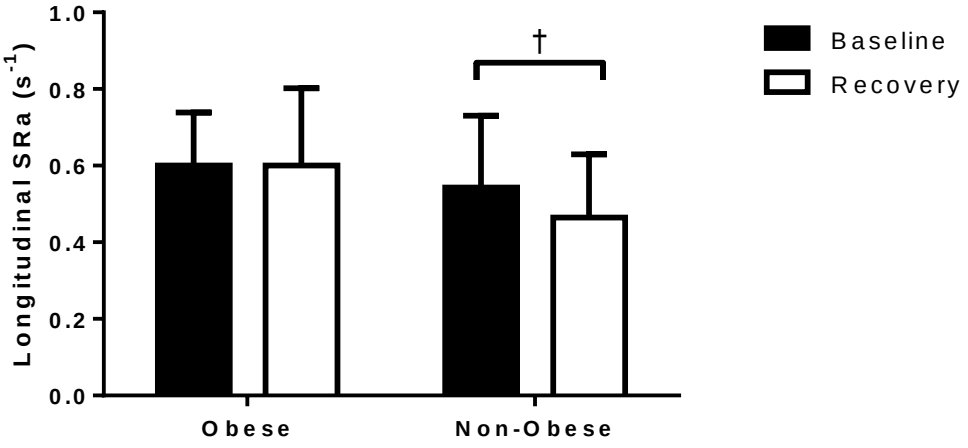

Figure 5. 12 Longitudinal SRa after 5-min recovery following heavy intensity exercise in obese and non-obese women. At 5-min recovery, LongSRa was lower than rest in the non-obese group with no change in the obese group. Time by group interaction, P > 0.05. † indicates a close to significant difference (P < 0.08).

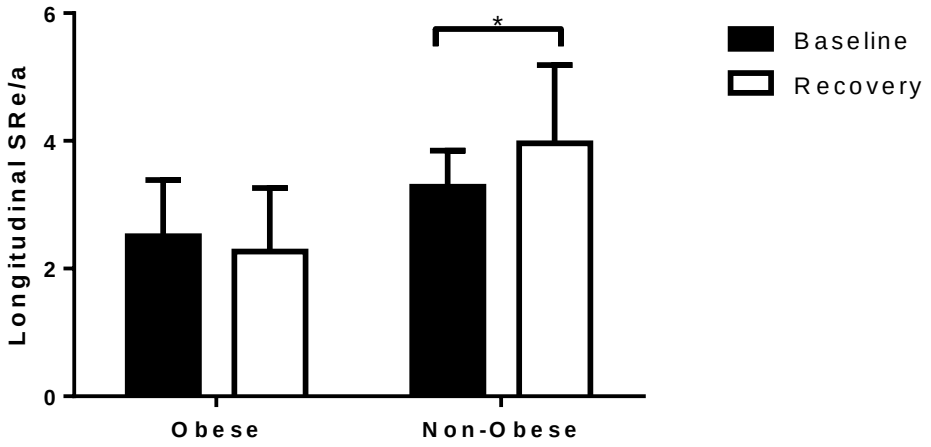

Figure 5. 13 Longitudinal SRe/a after 5-min recovery following heavy intensity exercise in obese and non-obese women. At 5-min recovery, LongSRe/a was higher than rest in the non-obese group with no change in the obese group. Time by group interaction, P > 0.05. * indicates a significant difference (P < 0.05).

5.4 Discussion

To the best of our knowledge, this is the first study to explore the LV systolic and diastolic functional responses to heavy-intensity exercise in healthy obese women using standard, TDI and 2DST echocardiography. It is also the first study to assess cardiac function during an exercise session defined according to LT as opposed to VO_{2max} or HR_{max}. The principal findings were that, during heavy-intensity exercise: (1) Obese women displayed a significantly higher systolic BP during exercise than non-obese women, but both groups showed similar changes in HR, SV and CO. (2) Obese women displayed significantly higher exercise-induced increase in diastolic myocardial velocity and systolic radial strain rate than non-obese women. Additionally, at 5-min recovery following heavy-intensity exercise: (1) Obese women displayed a slower HR recovery than non-obese counterparts. (2) Non-obese women displayed a post-exercise increase in diastolic function, not observed in obese women.

5.4.1 LV haemodynamic response to high-intensity exercise

During aerobic exercise, the intravascular blood volume increases in order to meet the metabolic demands of the exercising muscles. This occurs through arteriolar vasodilataion and decrease in peripheral vascular

resistance with a subsequent increase in systemic venous return to the heart (Rowland, 2008). The LV haemodynamic response to exercise generally mirrors these intravascular haemodynamic changes showing a parallel increase in heart rate, stroke volume, cardiac output and ejection fraction (Rowland, 2008).

In this study, we showed similar LV haemodynamic response in obese and non-obese women during heavy-intensity supine cycling at 120% LT except for SBP. Despite having similar resting SBP, a significantly higher exercise-SBP was observed in obese compared to non-obese women. High SBP during exercise has been shown to be is a strong predictor of hypertension and a stronger predictor of cardiovascular mortality than resting SBP in adults (Goble and Schieken, 1991, Mundal et al., 1994). This manifestation confirms that exercise reveals subtle unfavourable changes in cardiovascular function, not detected at rest. However, both groups displayed a similar exercise-induced increase in HR, SV, CO and EF. This is in line with previous reports showing similar exercise-induced increase in CO, SV and HR during incremental (Giordano et al., 2003) and steady (Salvadori et al., 1999, Vella et al., 2009) exercise in obese and non-obese individuals. However, this is in contrast to previous reports by (Rowland et al., 2003) showing higher CO during exercise in obese than non-obese girls. These girls however had higher resting CO than lean counterparts, which is in contrast to our participants who had similar haemodynamic parameters at rest. Reports on LV EF response to exercise thus far have been disparate. According to (Sasso et al., 2005) overweight and obese adults had a smaller increase in EF than lean controls during exercise, despite having higher EF at rest. However, (Ferraro et al., 1996) reported no change in EF in severely obese adults during submaximal exercise. Interestingly, (Alpert et al., 1989) showed that, in morbidly obese adults, only those who had normal LVM displayed an 11% increase in EF during exercise as opposed to those with LVH that showed no change in EF during exercise. Several factors may influence EF during exercise including preload, afterload and state of myocardial contractility. However, EF is known to be strongly influenced by haemodynamic changes and therefore it is not a reliable indicator of myocardial contractile response to exercise.

At 5 min post-exercise, a delay in heart rate recovery (HRR) was observed in obese compared to non-obese women. HRR is believed to be associated with vagal tone reactivation post-exercise (Arena et al., 2010) and a delayed HRR following strenuous exercise is a sign of impaired vagal reactivation

and has been shown to be strongly related cardiovascular risk factors in obesity (Mora et al., 2005). Impaired vagal reactivation is a manifestation of autonomic dysfunction resulting from insulin resistance and hyperinsulinemia associated with obesity (Carroll et al., 2012). Therefore, in our group of obese women, with high visceral adipose tissue content, the delay in HRR at 5 min post heavy-intensity exercise, compared to non-obese subject may be an early sign of insulin resistance.

5.4.2 Left ventricular systolic myocardial velocity, deformation and torsion during heavy-intensity exercise

Healthy obese women showed a similar exercise-induced increase in Sm as non-obese women. This is in line with reports by (Schuster et al., 2012) showing similar Sm in obese and non-obese children during an incremental exercise test. However, this is in contrast to reports by (Ingul et al., 2010) showing significantly lower Sm at rest and during exercise in obese compared to non-obese adolescents. The difference in the magnitude of change in Sm during exercise between both groups was not reported. Systolic myocardial velocity is generally dependent on both myocardial contractility and heart rate. Both these measures increase during exercise in response to sympathetic stimulation (Quintana et al., 2005). Therefore, impaired LV systolic myocardial velocity during exercise in obese subjects may be a reflection of contractile or autonomic dysfunction.

To the best of our knowledge, this is the first study to explore the changes in LV deformation in all 3 directions; longitudinal, circumferential and radial, and torsion during heavy intensity exercise in healthy obese women. We report a similar increase in global LV longitudinal, circumferential and radial strain in obese and non-obese women. However, higher RadSRs was observed during exercise in obese women, whereas LongSRs and CircSRs were similar in both groups. This was still manifested at 5 min recovery post-exercise. Additionally, a positive correlation was observed between both BMI and WC and the magnitude of increase in RadSRs during exercise. This possibly reflects an enhanced LV systolic function as a means of optimising adequate SV and CO for muscle perfusion and to overcome the high SBP during exercise. This is in line with previous reports by (Schuster et al. 2012) showing higher Sm in mildly obese compared to lean children at submaximal and maximal exercise despite both groups displaying similar Sm at rest and lower exercise intensities during an incremental exercise test. Interestingly, this was not observed in more severely obese children, indicating that only

mild degree of obesity is associated with a compensatory increase in LV systolic function during heavy-intensity exercise.

Strain is defined as the degree of deformation (ie. change in length) of a given myocardial segment compared to its end-diastolic length, and strain rate is the rate of this deformation (Dandel et al., 2009). The myocardium is made up of a complex network of helically-orientated longitudinal and circumferential myocardial fibrils (Nakajima et al., 1985, Torrent-Guasp et al., 2001). Therefore, the deformation of each fibril during systole will result in shortening in the longitudinal and circumferential directions and thickening in the transmural or radial direction of an entire segment of myocardium (Dandel et al., 2009). Since the myocardium is incompressible, the thickening of the wall occurs as a result of shortening in order to maintain volume (Kato et al., 2010). Hence radial strain represents the magnitude of systolic thickening resulting from longitudinal and circumferential shortening of the overlapping myocardial fibrils. Weidemann showed that radial strain correlates with inotropic stimulation (Weidemann et al., 2002), however it does not take into account the temporal dimension ie. how long it takes for the myocardium to reach a particular magnitude of thickening. Furthermore, (Weidemann et al., 2002) reported a strong direct correlation between peak RadSRs and change in LV pressure (dP/dtime) which is the gold standard measure of global LV function. Additionally, RadSRs was constant despite the increasing HR on inotropic stimulation, indicating that it is HR independent and only reflects myocardial inotropic state. Therefore, Weidemann argued that radial strain rate is better and more reliable measure of contractile function than radial strain.

Surprisingly, although radial thickening represents the outcome of longitudinal and circumferential shortening, our results show that the change in RadSRs in the obese women does not parallel any changes in LongSRs and CircSRs. This can be explained by either the possibility that changes in LongSRs and CircSRs were too subtle to be detected by echocardiography. However, there is always a possibility of measurement error. Nevertheless, this has previously been reported in the literature. Indeed, (Nottin et al., 2008) reported lower RadSRs but similar LongSRs and CircSRs in athletes compared to sedentary controls. Furthermore, (Pons, 2014) reported lower LV radial strain despite higher circumferential and longitudinal strain in long-distance runners compared to sedentary controls. It was suggested that, the lower radial strain at rest represents a myocardial contractile reserve in

radial deformation which can be utilised during exercise to maximise LV response to exercise (Pons, 2014).

5.4.3 LV diastolic inflow and myocardial velocity and deformation during high-intensity exercise

Normally, during exercise LA pressure does not change; therefore the rate of LV filling is determined by both the suction effect of LV end systolic pressure and the rate of diastolic myocardial relaxation (Rowland, 2008). Hence, increased early diastolic filling velocity will compensate for the shortened diastolic filling time during exercise as heart rate increases. We show for the first time that healthy obese women display a greater increase in Em during heavy-intensity exercise compared to lean controls. We also report a greater decrease in DCT during exercise in obese women compared to lean counterparts. Interestingly, this persisted after exercise cessation as shown by the slightly reduced DCT at 5-min recovery in obese women. This possibly reflects an enhanced LV diastolic filling during heavy-exercise to optimise adequate CO and SV for muscle perfusion during heavy-intensity exercise in addition to excess adipose tissue. This is further supported by the significant positive correlation observed between exercise-delta Em and both WC and BMI and the negative correlation observed between exercise-delta DCT and BMI. Previous reports by (Schuster et al., 2012) showed that obese children had significantly higher Em during exercise than non-obese controls. However, this was also observed at rest, indicating that it was not an influence of exercise, but rather a manifestation of excess adipose tissue in this cohort.

Interestingly, at 5-min recovery, non-obese women were found to have higher E/A ratio, LongSRe/a and RadSRe/a than resting values, whereas this was not observed in the obese group. The exact explanation of this observation is not clear, however it reflects a slight improvement in diastolic function after heavy exercise in non-obese women that is absent in obese ones. These changes were not strongly significant and further tests on larger cohorts are needed to confirm this finding.

5.4.4 Conclusions

This study shows for the first time that overweight/obese women have an accentuated LV systolic and diastolic response to heavy-intensity exercise compared to non-obese women. Obesity, particularly visceral adiposity, was found to be associated with a greater increase in both RadSRs and Em and decrease in DCT during heavy-intensity exercise reflecting higher systolic

and diastolic function, possibly as a means of optimising an adequate cardiac output for muscle perfusion. Additionally, obese women displayed a significantly higher SBP during exercise, indicating a high risk of developing hypertension and an increased risk of cardiovascular mortality. Furthermore, a delayed HRR was observed in obese women following heavy-intensity exercise, possibly reflecting an impaired post-exercise vagal reactivation and autonomic dysfunction. Finally, this study reports for the first time evidence of enhanced LV diastolic function immediately following heavy-intensity exercise in non-obese women, which was absent in obese women. In conclusion, despite evidence of subclinical LV systolic and diastolic dysfunction in mild obesity, heavy-intensity exercise provides an effective method of enhancing cardiac function in overweight/mildly obese women, particularly in individuals struggling to reduce their weights and/or maintain their weight loss.

5.4.5 Limitations and future work

This study included a small number of participants, affecting the ability to draw firm conclusions from it. Further studies involving large cohorts are needed to validate the above findings. Additionally, this study is observational and does not give information on molecular mechanisms. Future animal studies or studies involving human tissue biopsies for the biochemical assessment of cardiac myocyte signaling pathways and electorphysiology during and immediately following exercise would give valuable information to support our observations. Moreover, this study only includes women and does not take into consideration other potentially relevant factors such as age, race and genetic factors.

With regards to echocardiographic limitations, this study involved the assessment of obese women, which can result in suboptimal image quality and affect the analysis of data. Additionally, exercise can affect image quality and result in insufficient visualisation of the LV walls. It can also affect probe positioning resulting in inadequate image planes. Finally, exercise echocardiography has to be performed in a narrow time-window due to the time-consuming nature of serial acquisition of different image planes (Eroglu et al., 2006). MRI can potentially overcome these obstacles and give higher degrees of sensitivity and accuracy.

Chapter 6 The impact of heavy-intensity interval and continuous aerobic training on left ventricular structure and function in overweight/obese women

6.1 Introduction

Long-term aerobic training and its benefits on cardiovascular function are well-established (Blomqvist and Saltin, 1983). Evidence has shown that aerobic exercise training induces favourable LV structural and functional adaptations in healthy non-obese subjects (Baggish et al., 2008, D'Andrea et al., 2007). As it was observed in Chapter 4, excess adipose tissue, particularly visceral fat, is associated with concentric LV pathological remodelling and reduced LV myocardial velocity and deformation in both systole and diastole. Unfortunately, weight loss represents a difficult challenge in many obese women and the maintenance of weight loss can also be an even bigger problem that weight loss itself. Protecting the heart from the detrimental effects of obesity does not solely depend on weight reduction. Long-term exercise alone, particularly at heavy-intensity, has been shown to be an effective means of protecting and even improving cardiac function in obese individuals without accompanying weight loss. Indeed, in the previous chapter, we have demonstrated that heavy-intensity exercise enhances LV systolic and diastolic function in obese women. Additionally, evidence has shown that aerobic exercise mediates favourable LV structural and functional adaptations in obese individuals without the need to reduce body weight through dietary modifications (Vogelsang et al., 2008, Schuster et al., 2012, Sijie et al., 2012, Schrauwen-Hinderling et al., 2010). Exercise intensity appears to be a strong contributing factor to the magnitude of exercise-induced benefit on the heart (Swain and Franklin, 2006) and protection against developing heart disease (Wisloff et al., 2006). Additionally, (Wisloff et al., 2007) demonstrated that 12 weeks of heavy-intensity interval training resulted in LV reverse remodelling and significant improvements in LV systolic and diastolic function, which moderate-intensity continuous training had failed to achieve, in heart failure patients. With regards to obesity, (Ingul et al., 2010) showed that, 13 weeks of Heavy-intensity interval training were able to restore LV systolic and diastolic

function in obese adolescents to levels comparable to non-obese controls. However, other interventional studies involving low- (Eriksson et al., 2010) or moderate-intensity training (Millen et al., 2014) have failed to detect any change in LV structure or function in healthy obese individuals. From these observations, it seems that interval training may provide more beneficial outcomes on LV structure and function than continuous training because of the high-intensities achieved during the exercise intervals. It was observed in Chapter 5 that LV systolic and diastolic response to heavy-intensity exercise is higher in obese than non-obese women, suggesting a greater cardiac effort to optimise adequate cardiac output for muscle perfusion. This also suggests that heavy-intensity training maximises the cardiac benefit from exercise in obese individuals. It is not clear, however, whether the repetitive pattern of interval training provides any additional benefit on LV structural and functional adaptations to exercise training. To date, a comparison between work- and intensity-matched interval and continuous training on LV structure and function has not been studied. Therefore, the aim of this study is to compare work- and intensity-matched interval and continuous training on LV structural and functional adaptations in overweight/obese women. It is hypothesised that heavy-intensity continuous training will provide similar LV structural and functional adaptations to high-intensity interval training.

6.2 Methods

6.2.1 Participants

Twenty healthy overweight/obese females (age: 42 ± 5 yrs; BMI ≥ 27 kg/m^2 and/or WHR > 0.8) participated in the study. Recruitment was carried out through local poster advertisements in the University of Leeds campus and by contacting participants from previous studies, who had given permission to be contacted for further studies. All participants demonstrated low risk of subclinical coronary heart disease; they were non-smokers with no history of hypertension and were not utilising any form of prescribed medication. The nature and purpose of the study were explained to each participant and written informed consent was provided prior to their participation. All participants met the inclusion criteria outlined in the general methods chapter.

6.2.2 Experimental protocol

Initially, participants were invited to attend the exercise physiology laboratory at the University of Leeds on two occasions. During the first visit, the assessment of body composition was carried out and participants were given a chance to familiarize themselves with the study equipment. On the second visit, baseline echocardiography was performed followed by a cardiopulmonary fitness test for the assessment of maximal aerobic capacity (VO_{2max}) and the lactate threshold (LT) in order to calculate the appropriate work rates (WR) for the subsequent exercise sessions. Control factors for these two visits are detailed in the general methods (Chapter 3, section 3.2). Participants were then matched for age and BMI and randomly assigned to either an interval (INT, n = 10) or continuous (CON, n = 10) heavy-intensity exercise training group. Participants attended the University of Leeds exercise physiology laboratory twice per week for supervised exercise sessions, in addition to one home-based unsupervised exercise session once per week. At mid-point (ie. 6 weeks) in the exercise training programme, a training session was replaced by a cardiopulmonary fitness test in order to assess any change in VO_{2max} and LT and adjust exercise session work-rates accordingly. Following 12 weeks of training, echocardiography and cardiopulmonary fitness tests were completed within one week of the last training session.

6.2.3 Measured variables pre and post-training

The protocols for the following variables are described in detail in the general methods chapter.

6.2.3.1 Anthropometric variables

Anthropometric measurements were taken pre and post-training and included body mass (BM), height (HT), waist circumference (WC), hip circumference (HC), waist to hip ratio (WHR), fat mass (FM), fat percent (FP) and fat-free mass (FFM).

6.2.3.2 Echocardiographic variables

Echocardiographic assessment of LV structure and function is explained in detail in the general methods (Chapter 3, section 3.4). Echocardiography was completed at pre and post-training and included standard 2-D, PW, TDI and 2D-speckle tracking echocardiography. Standard 2D echocardiographic measurements included left ventricular internal diastolic diameter during systole and diastole (LVIDds and LVIDd respectively), posterior wall thickness during systole and diastole (PWTs and PWTd respectively), interventricular septal thickness during systole and diastole (IVSTs and IVSTd respectively), relative wall thickness (RWT), left ventricular mass (LVM), ejection fraction (EF), end-systolic, end-diastolic and stroke volumes (ESV, EDV and SV respectively). Doppler echocardiographic variables included early diastolic inflow velocity (E), late diastolic inflow velocity (A), E:A ratio (E/A), isovolumic relaxation time (IVRT), deceleration time (DcT), early diastolic myocardial velocity (Em), late diastolic myocardial velocity (Am), Em:Am ratio, E/Em ratio and myocardial performance index (MPI). Finally, 2-D speckle tracking echocardiographic variables included longitudinal strain (LongS), longitudinal systolic, early and late diastolic strain rates (LongSRs, LongSRe and LongSRa respectively), circumferential strain (CircS), circumferential systolic, early and late diastolic strain rates (CircSRs, CircSRe and CircSRa respectively), radial strain (RadS), radial systolic, early and late diastolic strain rates (RadSRs, RadSRe and RadSRa respectively), and torsion (LVtor).

6.2.3.3 Cardiopulmonary fitness

An incremental cycle ergometer ramp test in the seated position was performed at pre and post-training to determine peak oxygen uptake (VO_{2peak}),LT, their corresponding work-rates (WR_{peak} and WR_{LT}) and the individual work-rates for the subsequent exercise training sessions (Chapter 3, section 3.5).

6.2.4 Exercise training protocol

Both groups completed 12 weeks of work-matched heavy intensity exercise training consisting of cycling on a cycle ergometer (Lode BV, Excalibur Sport V2.0, the Netherlands) twice weekly under supervision at the University of Leeds exercise physiology laboratory. Additionally, participants were instructed to carry out one additional exercise session once weekly consisting of 30 min of unsupervised brisk walking. To ensure participants

trained at the intended intensity, first training sessions were monitored for VO_2 and blood lactate levels throughout the session. VO_2 levels were obtained by breath by breath data collection. Blood lactate levels were obtained by capillary blood sample collection using an automated blood lactate analyser (Lactate Pro, Arkray, Japan). Capillary blood samples were taken twice at rest, separated by a 5 min interval, for calculating the average, and every 5 min for the INT group and 4 min for the CON group as session duration was shorter as will be explained in detail below. After 6 weeks of training, cardiopulmonary exercise tests were performed on all participants and the work rates at which they cycled were adjusted to ensure they trained at the desired intensity as training adaptations occurred. An additional non-exercising control group was not included as the primary aim of this study was to compare the influence of two different exercise interventions (interval and continuous) on cardiac structure and function in obese women as opposed to the impact of exercise alone.

6.2.4.1 Interval training sessions

Interval training sessions consisted of a modification of the 1:2 (work:recovery) duty cycles first developed by (Turner et al., 2006). In this study, Turner *et al.* compared the physiological responses to 4 different duty cycles at work:recovery ratios of 10:20, 30:60, 60:120 and 90:180s by monitoring VO_2 and blood lactate levels throughout each session. All 4 sessions were work matched and consisted of 30 min of cycling on a cycle ergometer at 120% WR_{peak} with recovery periods at 20 W. The results showed that the 30:60s duty cycle corresponded to the heavy-intensity domain as demonstrated by a rising VO_2 level reaching a plateau above the LT at ~10-15 min and a rising blood lactate level reaching a plateau from ~10 min. In our study, the interval training sessions were modified and consisted of 40:80s duty cycles of cycling at 70% delta work-rate (70% ΔWR) for 40s followed by active recovery at 20 W for 80s. 70% ΔWR is 70% of the difference between WR_{peak} and WR_{LT} and is calculated as:

$$70\%\ \Delta WR = 0.7(WR_{peak} - WR_{LT}) + WR_{LT}$$

The reason for normalising to ΔWR rather than WR_{peak} or VO_{2max}, as done by most exercise training studies, is that normalising for ΔWR takes into account individual differences in LT whereas normalising to WR_{peak} or VO_{2max} can put individuals at different points above or below LT. The WR of 70% ΔWR was chosen as it is above critical power *ie*. in the very heavy intensity domain (Cannon et al., 2011). Finally, the work:recovery ratio of

40:80s was chosen as it was confirmed in a pilot session to be in the heavy intensity domain and with a slightly higher VO2-time integral and average VO_2 than 30:60s, hence maximising the influence of exercise training (Figure 6.1). The duration of the interval sessions in the first week was 20 min, increased to 25 min in week 2, 30 min in week 3, 35 min in week 7 and 40 min in week 10.

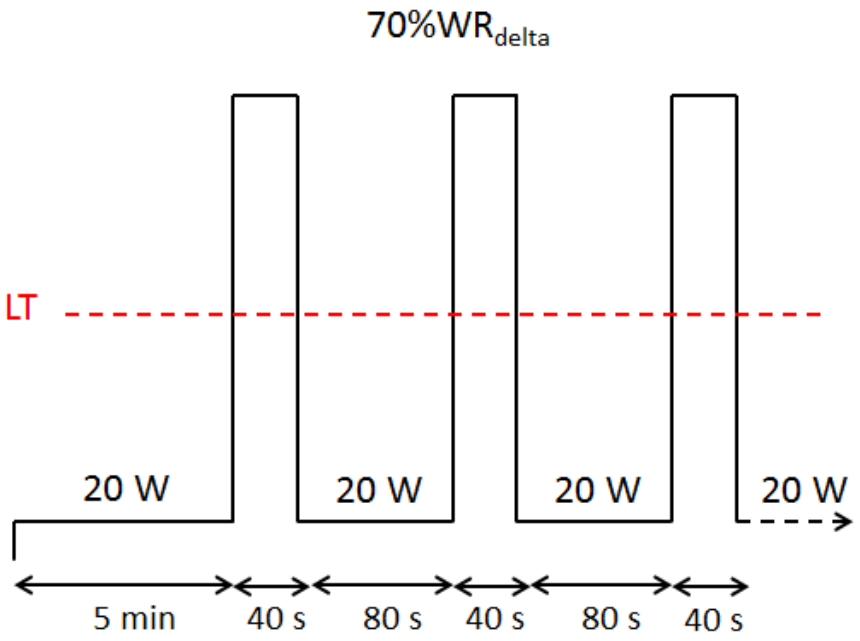

Figure 6. 1 Schematic representation of the heavy-intensity interval training session. Interval training sessions consisted of 40:80 s duty cycles at 70%WR_{delta} which was above lactate threshold (LT; red shaded line), followed by 20W active recovery for a duration of 20 min.

6.2.4.2 Continuous training sessions

The CON training sessions consisted of continuous steady cycling at 20% ΔWR for a pre-calculated duration that would give the same total amount of work achieved if the individual was to perform an INT session (Figure 6.2). This was done by calculating the total amount of work (J) that would be achieved by this individual if they were to perform an INT session at 70% ΔWR for 40s and 20W for 80s for the duration of 20 – 40 min depending on the time point of the training. Then this total amount of work was divided by this individual's work rate (20% ΔWR). This was to ensure both groups were matched for the amount of work and both fell in the heavy intensity domain.

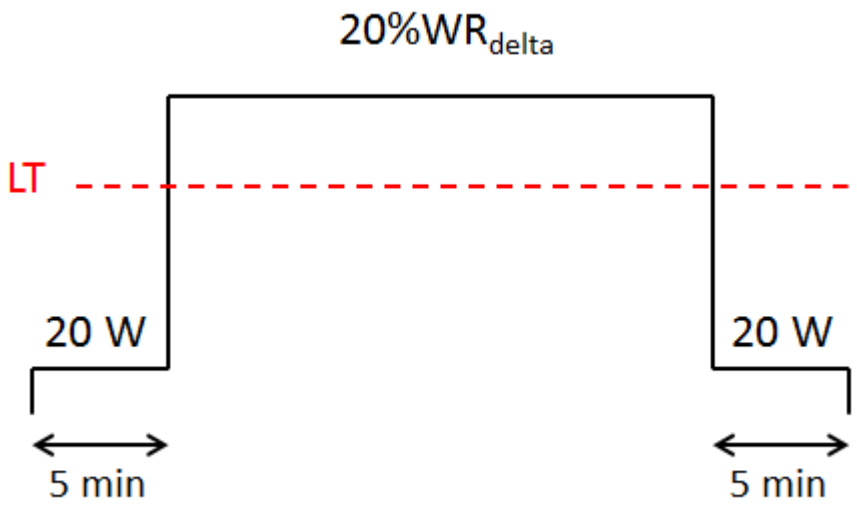

Figure 6. 2 Schematic representation of the heavy-intensity continuous training exercise session. Continuous training sessions consisted of continuous cycling at 20%WR_{delta} which was above lactate threshold (LT; red shaded line) for a pre-calculated period of time that would result in a total amount of work equivalent to an interval training session.

6.2.5 Statistical analysis

All data were normally distributed and were presented as mean ± SD. The effects of training were analysed using ANOVA with repeated measures with time (pre and post) entered as the within subjects factor and training group (INT and CON) as the in-between subjects factor. At baseline, a significant difference was observed between both groups' LVPWd, Am and CircSRs. Therefore, baseline values for these variables were entered as covariates to the ANOVA test. Where significant time by group interaction was found, a paired t-test was performed to assess the significance of change in each group. The percentage change from pre- to post-training was assessed for group differences using a Student's independent t-test. Significance was accepted if $P < 0.05$.

6.3 Results

6.3.1 Exercise session characteristics

The exercise session characteristics for both groups are presented in Table 6.1. The INT group exercised at higher WR than CON group for a longer period of time per session. However the total amount of work per session was similar between both groups.

Table 6. 1 First session characteristics (mean ± SD) for interval and continuous exercise training

	Interval	Continuous
WR_{LT} (W)	57 ± 15	68 ± 14
Session WR (W)	124 ± 25	85 ± 16 *
Work/session (KJ)	66 ± 10	67 ± 9
Session durations (min)	20	13.3 ± 1.3 *

* indicates a significant difference between both groups ($P < 0.01$)

6.3.2 Participants' characteristics

Two participants only completed 10 weeks of training; one from the INT group due to injury not related to training and one from the CON group due to unavailability. In these two participants, the sessions' durations were adjusted to give a total amount of work equal to 12 weeks of training. All other participants completed the 12 weeks of training. The anthropometric, BP and HR characteristics of the 2 groups are presented in table 6.2. There was no significant difference between both groups' baseline anthropometric measurements, cardio-respiratory fitness and BP before and after training. Twelve weeks of training did not have any significant effect on participants' anthropometric characteristics in either groups. With regards to BP, there was a trend for a decrease in SBP post-training in both groups (time effect $P = 0.08$, time by group interaction $P > 0.05$).

Table 6. 2 Anthropometric, BP, HR and cardiopulmonary fitness measurements (mean ± SD) of the interval and continuous training groups before and after 12 weeks of training

	Interval		Continuous	
	Pre	Post	Pre	Post
Weight (kg)	88.5 ± 15	86.9 ± 16	85.3 ± 12	85.7 (12.6)
Height (m)	1.64 ± 0.1	1.64 ± 0.1	1.66 ± 0.1	1.66 (0.1)
BMI (kg/m^2)	32.6 ± 3.3	32 ± 3.6	30.9 ± 3.7	31 (3.7)
Waist (cm)	106.2 ± 7.3	103.7 ± 10.6	101.4 ± 9.5	101.9 (10.6)
WHR	0.90 ± 0.1	0.89 ± 0.1	0.90 ± 0.1	0.90 ± 0.1
Fat mass (kg)	39 ± 7.9	38.4 ± 9.5	35.3 ± 8.5	36.1 (8.3)
Fat-free mass (kg)	49.3 ± 7	48.5 ± 7	49.8 ± 5.1	49.5 (5.2)
SBP (mmHg)	124 ± 11	119 ± 7	125 ± 15	124 ± 15
DBP (mmHg)	81 ± 9	79 ± 8	82 ± 10	82 ± 10
MAP (mmHg)	96 ± 10	92 ± 8	96 ± 11	96 ± 11
Resting HR (bpm)	68 ± 6	68 ± 11	66 ± 10	68 ± 7
VO_{2max} (ml/kg/min)	24.1 ± 2.9	25.3 ± 3.3	24.6 ± 2.7	25.7 ± 2.3
LT (ml)	1077 ± 187	1169 ± 247	1181 ± 239	1181 ± 183

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, VO_{2max} = maximal oxygen uptake, LT = lactate threshold.. No significant time effect ($P > 0.05$) on anthropometric, BP and HR measurements after 12 weeks of training. A trend for a reduction in SBP was noticed in both groups (time effect $P = 0.08$)

6.3.3 Left ventricular structure

Table 6.3 displays both groups' measures of LV structure before and after 12 weeks of training. At baseline, the CON group displayed significantly higher PWTd, being compared to the INT group ($P < 0.05$). No significant difference was observed between both groups' IVSTd, LVIDd, LVM and RWT ($P > 0.05$), however the CON group displayed higher mean LVM and RWT than the INT group with large effect sizes ($d = 0.5$ and 0.6 respectively). Moreover, the CON group's mean LVM and PWTd exceeded the limits for normality (LVM > 162 g, PWTd > 0.9 cm) as per the American Society of Echocardiography guidelines (Lang et al., 2005), whereas the INT groups' mean LVM and PWTd were within normal limits. Finally, both groups showed evidence of concentric remodelling (RWT > 0.42) at baseline, being more marked in the CON compared to the INT group though not significantly different ($P > 0.05$; effect size $d = 0.6$).

Table 6. 3 LV structure (mean ± SD) after 12 weeks of either interval or continuous training in overweight/obese women

	Interval		Continuous	
	Pre	Post	Pre	Post
LVM (g)	146.5 ± 35.7	154.8 ± 40.1	166.6 ± 43.5	151.5 ± 32.7
LVID (cm)	4.35 ± 0.49	4.33 ± 0.62	4.28 ± 0.51	4.44 ± 0.36
IVS (cm)	1.08 ± 0.19	1.09 ± 0.18	1.02 ± 0.13	1.0 ± 0.09
PWT (cm)	0.90 ± 0.15	0.99 ± 0.25	1.18 ± 0.24 †	0.99 ± 0.16 *
RWT	0.46 ± 0.1	0.49 ± 0.12	0.52 ± 0.09	0.45 ± 0.08 *

LVM = Left ventricular mass, LVID = LV internal diameter, IVS = inter-ventricular septal thickness, PWT = posterior wall thickness, RWT = relative wall thickness. No significant main time effect in LV structure after 12 weeks of training. † = significantly different from the other group at the same time point. * = significantly different from pre-training in the same group.

After 12 weeks of training, opposite changes were observed in both groups' PWTd (time effect $P > 0.05$, time by group interaction $P < 0.05$), LVM and RWT (both, time effect $P > 0.05$, time by group interaction $P = 0.06$). Post-hoc analysis revealed ~16%, ~6% and ~12% decreases in PWT, LVM and RWT respectively in the CON group post-training ($P < 0.05$, except for LVM; effect size $d = 0.4$). As for the INT group, a 10% increase in PWTd ($P > 0.05$, $d = 0.4$) and a 6% increase in LVM and RWT (both $P > 0.05$, $d = 0.3$) were observed with no change in RWT (Figure 6.3a, c and e). Furthermore, significant inverse correlations were observed between baseline PWT, LVM

and RWT and their respective changes pre to post-training ($r = -0.64$ $P < 0.05$, -0.54 $P < 0.05$ and -0.40 $P = 0.09$ respectively; Figure 6.3b, d and f). It was noted that participants with baseline PWTd and LVM above normal almost invariably increased in these measures post-training and vice versa. Interestingly, after 12 weeks of training, the CON group's mean LVM and PWTd were no longer above normal limits according to ASE guidelines (Lang et al., 2005). Finally, there was no significant change in LVID in either group after 12 weeks of training (time effect $P > 0.05$, time by group interaction $P > 0.05$).

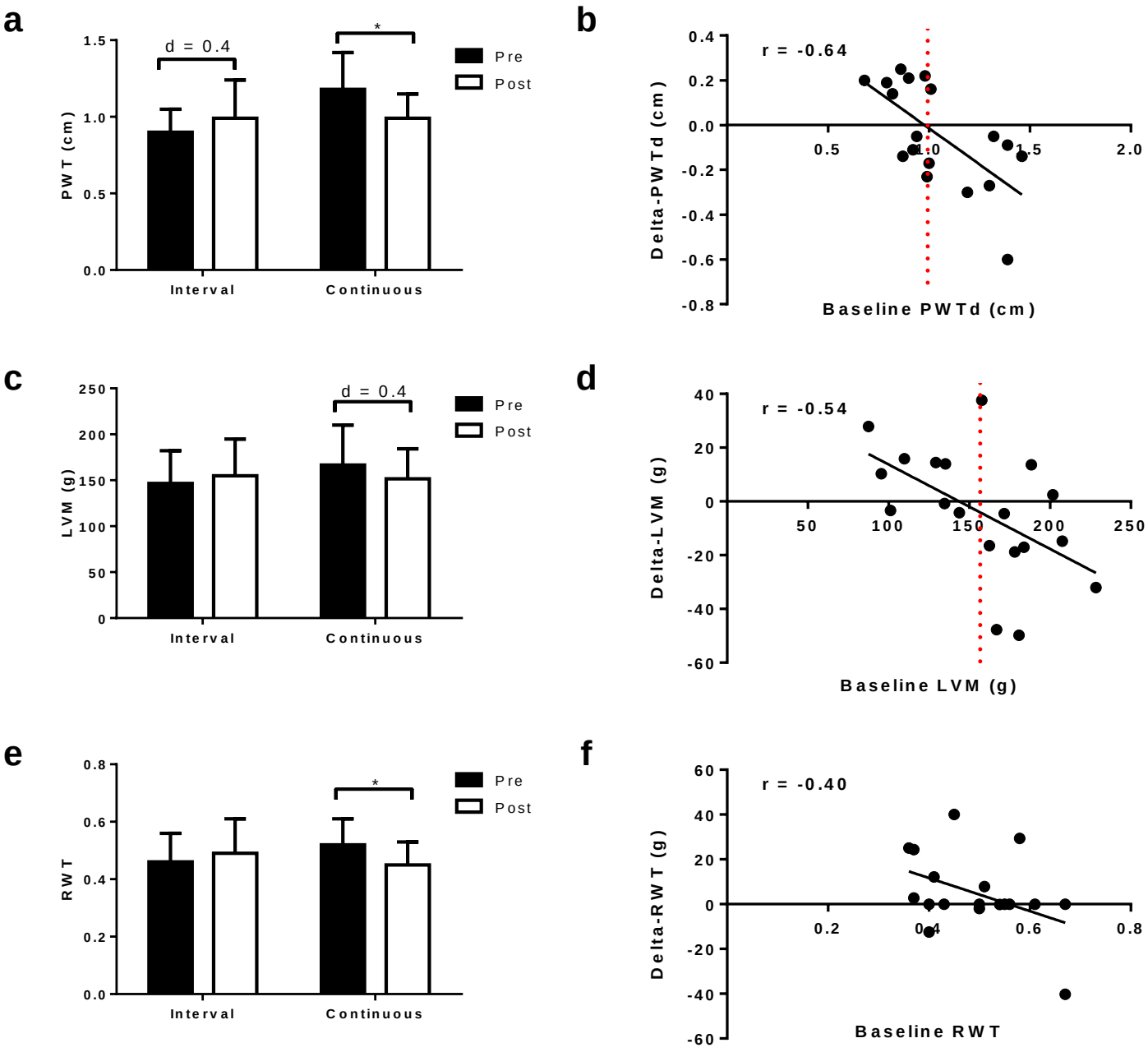

Figure 6. 3 Figure 5. 1 Changes in LV posterior wall thickness (PWTd), mass (LVM) and relative wall thickness (RWT) after 12 weeks of interval (INT) or continuous (CON) heavy-intensity training in obese women. (a) PWTd increased in the INT group whereas and decreased in the CON group post-training (time by group interaction $P < 0.05$). (b) LVM decreased in the CON group post-training whereas it did not change in the INT group (time by group interaction $P = 0.06$) (c) RWT decreased in the CON group post-training whereas it did not change in the INT group (time by group interaction $P = 0.06$). Inverse correlations were observed between (c) baseline PWT and pre to post delta-PWT ($P < 0.05$), (d) baseline LVM and pre to post delta-LVM ($P < 0.05$) and (e) baseline RWT and pre to post delta-RWT ($P = 0.09$). The red dotted lines represent the cut-offs for normality according to the ASE guidelines (Lang et al., 2005).

6.3.4 Left ventricular systolic function

At baseline, All measures of systolic function were not different between both groups (P > 0.05; Table 6.4). Twelve weeks of heavy-intensity interval and continuous training resulted in a 30% and 11% increase in CircS and LongSRs respectively and a 7% decrease in MPI (Time effect P < 0.05; Table 6.4) with no difference between both groups (time by group interaction P > 0.05). the percentage change in these variables in each group did not differ from the other group (P > 0.05). No change was observed in the remaining measures of systolic function in both groups (Time effect P > 0.05).

As shown in Figure 5.2a and c, trends for significant time by group interactions were detected for RadS (P = 0.09) and RadSRs (P = 0.05) with post-hoc analysis revealing a respective ~25% (P = 0.07) and ~19% (P > 0.05, effect size d = 0.6) post-training reductions in these variables in the CON group. As for the INT group, no change was observed in RadS, however RadSRs increased by ~11% (P > 0.05, effect size d = 0.5) post-training. Interestingly, significant correlations were found between the pre to post-training delta-PWTd and both delta-RadS and delta-RadSRs (r = 0.55 and 0.66 respectively, P < 0.05; Figure 5.2b and d).

Table 6. 4 LV systolic function (mean ± SD) before and after 12 weeks of heavy intensity training in obese females

	Interval		Continuous	
	Pre	Post	Pre	Post
SV (ml	69.5 ± 11.4	69 ± 9.9	69.7 ± 7.06	74.7 ± 8.61
EF (%)	79.7 ± 9.95	77.4 ± 7.66	80.1 ± 5.9	80.8 ± 6.14
HR (bpm)	71.3 ± 10.3	72.3 ± 11.9	71.9 ± 9.54	66.7 ± 7.3
CO (L)	4.7 ± 0.63	4.89 ± 0.46	4.96 ± 0.44	4.93 ± 0.44
FS	0.39 ± 0.08	0.38 ± 0.08	0.38 ± 0.08	0.41 ± 0.08
Sm (ms)	6.66 ± 2.24	7.47 ± 2.17	6.89 ± 1.82	7.46 ± 2.13
LongS (%)	20.4 ± 1.28	20.7 ± 3.75	18.8 ± 3.02	19.2 ± 2.96
CircS (%)	14.7 ± 2.21	27.8 ± 4.35*	15.4 ± 3.85	21.5 ± 6.84*
RadS (%)	54 ± 17.4	54 ± 21	45.2 ± 17.7	31.4 ± 16.6†
LongSRs (s^{-1})	1.02 ± 0.1	1.14 ± 0.21*	0.98 ± 0.13	1.09 ± 0.28*
CircSRs (s^{-1})	1.24 ± 0.14	1.22 ± 0.19	1.29 ± 0.25	1.23 ± 0.34
RadSRs (s^{-1})	2.15 ± 0.4	2.33 ± 0.33	2.04 ± 0.54	1.64 ± 0.74
Torsion (%)	14.2 ± 5.59	15.1 ± 7.36	15.4 ± 6.04	14.1 ± 6.75
MPI	0.34 ± 0.04	0.31 ± 0.05*	0.33 ± 0.04	0.31 ± 0.02*

SV = stroke volume, EF = ejection fraction, HR = heart rate, COP = cardiac output, FS = fractional shortening, S' = systolic myocardial velocity, LS = longitudinal strain, CS = circumferential strain, RS = radial strain, LSRs = longitudinal systolic strain rate, CSRs = circumferential systolic strain rate, RSRs = radial systolic strain rate, MPI = myocardial performance index. * indicates significant difference from pre-training in the same group ($P < 0.05$). † indicates close to significant difference from pre-training in the same group.

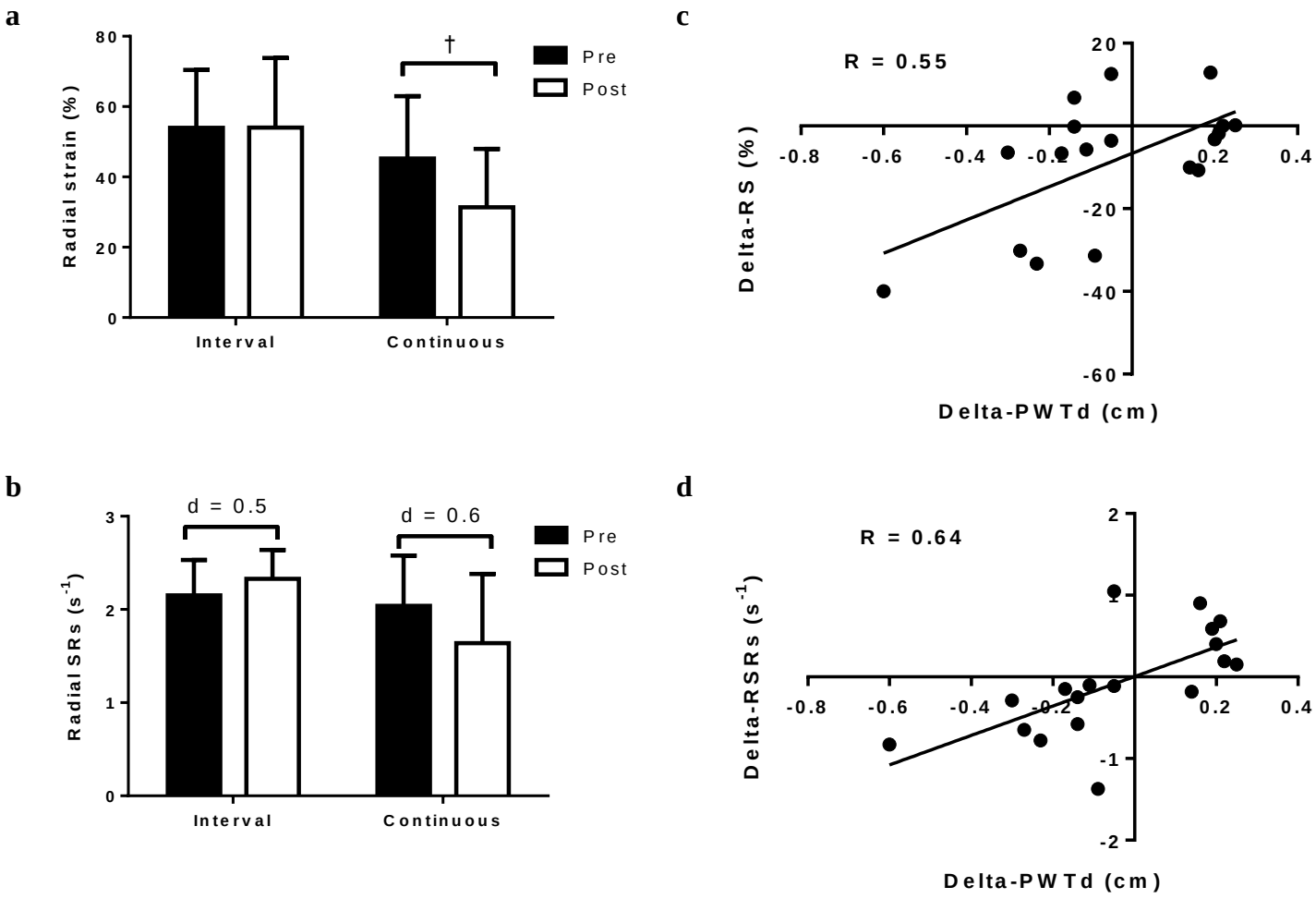

Figure 5. 14 Changes in left ventricular posterior radial strain and systolic strain rate after 12 weeks of interval (INT) or continuous (CON) heavy-intensity training in obese females. (a) Radial strain decreased in the CON group post-training with no change in the INT group (time by group interaction P = 0.09). (b) Radial SRs decreased in the CON group and increased in the INT group post-training (time by group interaction P = 0.05). Significant positive correlations were observed between pre to post-training delta-PWT and (c) delta-radial strain (P < 0.05) and (d) delta-radial SRs (P < 0.05). d indicates cohen's effect size.

6.3.4 Left ventricular diastolic function

At baseline, both groups had similar measures of LV diastolic function (P > 0.05; Table 6.5). After 12 weeks of training, both groups demonstrated a general improvement in diastolic function represented by an increase in Em by ~30%, Em/Am by ~86%, CircSRe by 18% and CircSRa by 45% and a decrease in Am by ~26% (time effect P < 0.05, except CircSRe P = 0.07;

time by group interaction > 0.05). A significant time by group interaction was observed for RadSRe ($P < 0.05$) with post-hoc analysis showing a ~15% decrease in the CON group ($P = 0.08$) and a ~12% increase in the INT group post training ($P > 0.05$, $d = 0.5$) (table 5.4). No other time by group interactions were observed in the rest of the diastolic measures ($P > 0.05$). Interestingly, a significant correlation was observed between pre to post delta-RadSRe and delta-PWTd ($r = 0.49$, $P < 0.05$).

Table 6. 5 Changes in LV diastolic function (mean ± SD) after 12 weeks of heavy intensity training in obese females

	Interval		Continuous	
	Pre	Post	Pre	Post
E (ms)	0.89 ± 0.15	0.95 ± 0.16	0.85 ± 0.22	0.87 ± 0.16
A (ms)	0.57 ± 0.12	0.60 ± 0.13	0.63 ± 0.13	0.61 ± 0.11
E/A ratio	1.69 ± 0.63	1.65 ± 0.46	1.37 v 0.33	1.48 ± 0.50
DCT (ms)	184 ± 45	193 ± 32	189 ±40	196 ± 20
IVRT (ms)	93.1 ± 11.7	87.9 ± 15.8	113.6 ± 7.7	91.9 ± 9.0
Em (ms)	6.99 ± 0.68	8.77 ± 2.4*	6.35 ± 0.85	7.8 ± 1.91*
Am (ms)	9.23 ± 0.82	6.84 ± 2.84*	8.63 ± 1.07	6.41 ± 2.52*
Em/Am ratio	0.76 ± 0.12	1.37 ± 0.31*	0.74 ± 0.06	1.41 ± 0.67*
E/Em	0.13 ± 0.03	0.12 ± 0.05	0.13 ± 0.03	0.12 ± 0.04
LSRe (s^{-1})	1.43 ± 0.19	1.5 ± 0.38	1.32 ± 0.31	1.34 ± 0.3
CSRe (s^{-1})	1.17 ± 0.35	1.33 ± 0.36†	1.18 ± 0.31	1.44 ± 0.47†
RSRe (s^{-1})	1.71 ± 0.26	1.89 ± 0.46	2.09 ± 0.73	1.67 ± 0.37†
LSRa (s^{-1})	0.86 ± 0.14	0.88 ± 0.33	0.85 ± 0.18	0.86 ± 0.3
CSRa (s^{-1})	0.41 ± 0.19	0.65 ± 0.29*	0.46 ± 0.19	0.62 ± 0.26*
RSRa (s^{-1})	1.31 ± 0.62	1.5 ± 0.36	1.13 ± 0.34	1.22 ± 0.46

E, early mitral inflow velocity; A, late mitral inflow velocity; DCT, early inflow velocity deceleration time; IVRT, isovolumetric relaxation time; Em, early diastolic myocardial velocity; Am, late diastolic myocardial velocity; LongSRe, CircSRe and RadSRe, early diastolic strain rate in the longitudinal, circumferential and radial directions respectively; LongSRa, CircSRa and CircSRa, late diastolic strain rate in in the longitudinal, circumferential and radial directions respectively. * indicates a significant difference from pre-training in the same group ($P < 0.05$). † indicates a close to significant difference from pre-training in the same group ($P < 0.09$).

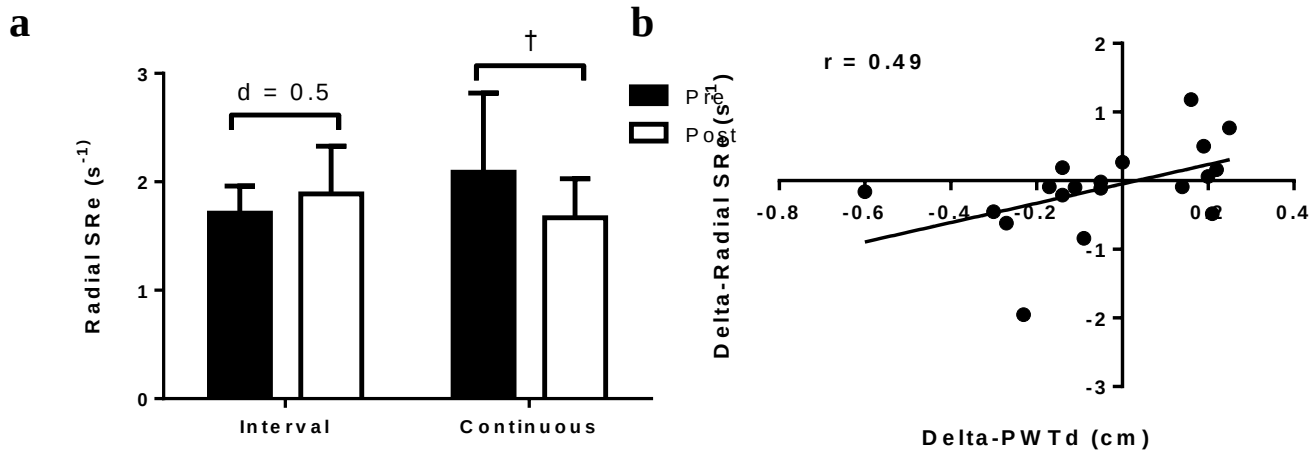

Figure 5. 15 Changes in early diastolic radial strain rate after 12 weeks of interval or continuous heavy-intensity training in obese females. (a) Radial SRe decreased by ~15% (P = 0.08) in the CON group, whereas it increased by ~12% (P > 0.05) in the INT group post-training (time by group interaction P < 0.05). (b) A significant direct correlation was observed between pre to post delta Radial SRe and delta PWTd (P < 0.05). d indicates Cohen's effect size. †indicates close to significance (P < 0.09).

6.4 Discussion

To the best of our knowledge, this is the first study to compare the effects of work-matched heavy-intensity continuous and interval exercise training on LV structure and function in overweight/obese women. The principal findings were that both exercise types induced similar improvements in LV systolic and diastolic function only detected by novel TDI and 2DST echocardiography however their impact on LV structure differed according to baseline LV size and morphology in each group.

6.4.1 Impact of aerobic exercise training on LV structure

Twelve weeks of heavy-intensity interval and continuous training induced opposite outcomes on LV structure. The continuous training group which displayed characteristics of pathological LV concentric hypertrophy at baseline, demonstrated a training-induced reverse remodelling following training, evidenced by a significant reduction in posterior wall thickness with subsequent reduction in LVM and RWT resulting in a non-hypertrophic LV with a significantly less concentric morphology. The interval training group, which had normal mean LVM at baseline, demonstrated a slight increase in posterior wall thickness, LVM and RWT after training with mild to moderate

effect size, though not reaching statistical significance. This could possibly indicate early signs of exercise-induced LV remodelling, represented in increased wall thickness preceding chamber dilatation. Aerobic exercise is known to induce eccentric LV hypertrophy *ie.* increase in both LV mass and internal diameter (Weiner and Baggish 2012). No change in LVIDd was observed in either groups, probably due to the short duration of training as it appears wall thickness changes precede diameter changes. Shuster et al. (2011) reported a significant reduction in LV wall thickness and mass following 8 weeks of low intensity aerobic training in obese men that had severe LV hypertrophy at baseline, whereas Vogelsang et al. (2008) reported a post-training increase in LVM after 4 months of moderate-intensity aerobic training in mild to moderately obese adults with normal pre-training LVM. Hence, it appears that the nature of morphological alterations in response to aerobic training vary according to the state of LV structure at baseline and how severe (if any) LV pathological remodelling is manifested. Other studies reported no change in LV structure following different aerobic training in healthy obese subjects with normal pre-training LVM. These training programmes included 6 months low-intensity training (Eriksson 2010), 8 months and 6 months moderate-intensity training programmes (Mitchell et al. 2002 and Stewart et al. 2005 respectively). Therefore, the heavy-intensity used in our study possibly explains the favourable changes, albeit small, in LV structure in the INT group despite having normal baseline LVM. Hence, the training intensity as well as the pathological state of the myocardium at baseline appear to be strong determinant of training-induced LV structural adaptations. Other factors include participants' state of physical fitness, gender, race and genetic factors (Weiner and Baggish 2012).

It is not possible to conclude from our results whether interval training is superior to continuous training or vice versa in improving LV structure because of the baseline structural differences between both groups. Matching subjects for LV size and morphology was not possible in this study due to the blinded nature of the analysis. A comparison between work-matched heavy-intensity interval and continuous training after matching subjects for LV size and morphology is necessary. Nonetheless, our results suggest that both exercise types resulted in favourable changes in LV structure after 12 weeks of heavy-intensity training.

Suggested mechanisms for exercise-induced LV remodelling and hypertrophy include increased insulin-like growth factor-1 (IGF-1) expression, activation of phosphoinositide-3 kinase (PI3K), down-regulation

of microRNAs with subsequent reduction in collagen and myocardial fibrosis, reduction of cardiac myocyte apoptosis and induction of cellular regeneration (Ellison 2012, Gielen 2010). Furthermore, exercise has been shown to enhance insulin sensitivity through activation of monophosphate-activated kinase (AMPK) which suppressed triglyceride and fatty acid synthesis and activates glucose uptake and glycogenolysis. Indeed, Stewart et al. (2005) reported a negative correlation between markers of insulin resistance and increase in LV size following 6 months of moderate intensity training in overweight and moderately obese healthy adults. In the context of obesity, all these mechanisms would counteract and reverse the mechanisms involved in pathological remodelling which would result predominantly in a reduction in LV wall thickness. In subjects without pathological remodelling, the predominant outcome of exercise on LV structure would be manifested as an increase in wall thickness and physiological hypertrophy. Both outcomes were manifested in our study by both interval and continuous heavy-intensity exercise training.

6.4.2 Impact of heavy-intensity interval or continuous training on standard echocardiographic measures of LV systolic and diastolic function

Twelve weeks of interval and continuous heavy-intensity training did not have any impact on standard echocardiographic measures of measures of LV systolic function including SV, EF and FS and diastolic function including E, A, E/A, IVRT and DCT in overweight and obese healthy women. Reports from the literature with regards to the influence of aerobic training on standard echocardiographic variables in obese healthy subjects have been variable. With regards to systolic function, Sijie et al. (2012) reported a significant increase in SV and EF in overweight young women following 12 weeks of either moderate/heavy-intensity aerobic training. Shrauwen et al. (2010) reported a significant increase in EF and SV following 12 weeks of moderate-intensity mixed endurance and resistance training in overweight and obese adult males, however these measures were assessed by MRI which is more sensitive and accurate than echocardiography (Greenberg 1997). As for diastolic function, Ingul et al. (2010) reported decrease in DCT and IVRT with no change in E, A and E/A ratio following 13 weeks of heavy-intensity interval training in 10 obese adolescents. Schuster et al. (2011) reported similar findings in 10 mildly obese adults after 8 weeks of low-intensity training. Several studies, however failed to detect any change in standard and/or TDI-derived echocardiographic measures of systolic and/or

diastolic function after aerobic training of a wide range of durations and intensities including 10 days moderate-intensity training in obese men and women (Baynard et al. 2008), 6 weeks of moderate intensity continuous or heavy-intensity interval training in obese adults (Millen et al. 2014), 8 months of moderate or heavy-intensity training in obese adolescents (Mitchell et al. 2014) and 4 months aerobic training at an average HR of 157 bpm in obese children (Humphries et al. 2002). As mentioned in previous chapters, standard echocardiography is highly dependent on preload and afterload and has a low sensitivity in detecting subclinical contractile dysfunction.

6.4.3 Impact of heavy-intensity interval or continuous training on TDI-derived myocardial systolic and diastolic velocity and myocardial performance index

Twelve weeks of heavy-intensity interval and continuous training resulted in an increase in Em, Em/Am and decrease in Am and MPI with no change in Sm in healthy overweight/obese women. Ingul et al. (2010) and Schuster et al. (2011) both reported increased Em following 13 weeks of heavy-intensity interval training in 10 obese adolescents and 8 weeks of low-intensity training in 10 mildly obese men respectively. Millen et al. (2014) did not observe any change in Em after 6 weeks of moderate intensity continuous or heavy-intensity interval training in obese men and women. Myocardial performance index is a fairly new load-independent TDI-derived measure of combined systolic and diastolic function that has been shown to be highly sensitive measure of cardiac dysfunction (Brush 200), strongly correlate with LV function derived from cardiac catheterization (dP/dt; Tei et al. 1997) and an independent predictor of congestive cardiac failure (Arnlov et al 2004). MPI has been shown to decrease following aerobic training in healthy non-obese subjects indicating an improvement in systolic and diastolic contractile performance (Tuzun 2014) however it has never been investigated in obese individuals. This is the first study to assess and report a positive impact of aerobic training on MPI in healthy overweight/obese women reflecting an improvement in intrinsic systolic and diastolic contractile performance.

6.4.4 Impact of heavy-intensity interval or continuous training on myocardial systolic and diastolic deformation and torsion

This is the first study to examine the impact of aerobic training on all 3 planes of motion (longitudinal, circumferential and radial) using 2DST echocardiography in healthy obese subjects. Twelve weeks of both heavy-intensity interval and continuous training resulted in an increase in global LV

longitudinal SRs, circumferential systolic strain and circumferential diastolic SRe and SRa. Schuster et al. (2011) previously reported an increase in global 2DST-derived longitudinal strain and SRs and SRe in mild to moderately obese men after 8 weeks of low-intensity continuous training. It was observed that, at baseline, the men involved in this study had severe LV hypertrophy (LVM = 234.6 ± 16.9 g) and lower longitudinal strain values compared to our values (15.9 ± 0.8 vs. 19.7 ± 2.3%) however, the longitudinal SRs were similar to our values. Ingul et al. (2010) also reported an increase in global longitudinal strain, SRs and SRe after 10 weeks of heavy-intensity interval training in mild to moderately obese adolescents. These two studies did not assess circumferential or radial deformation. Several factors can influence strain and strain rate, including preload, afterload, heart rate and cardiac myocyte contractility (Becker et al. 2007). In this study we report no change in EDV, E/Em ratio or SWS following training reflecting no change in preload or LV filling pressure or afterload respectively. Also, resting heart rate did not change following training. Therefore, the improved global longitudinal systolic and circumferential systolic and diastolic deformation are most likely reflections of improvement in cardiac myocyte contractility after training.

With regards to radial strain, SRs and SRe, only the continuous training group displayed a reduction in these measures post-training. As explained in the previous chapter, radial strain and strain rate represent the magnitude and rate of change in thickening or thinning of the myocardium in response to the longitudinal and circumferential shortening or lengthening of its helically oriented fibres during systole or diastole. This change in thickness occurs in order to maintain cardiomyocyte volume as the myocardium is incompressible in nature (Dandel 2009). Theoretically, this applies when cardiac myocyte length and width is constant. Hence, if the myocardium decreases in thickness, it would be reasonable to expect a parallel reduction in the degree of radial thickening or thinning in response to shortening or lengthening during systole or diastole. Our observation that the reduction in radial strain, SRs and SRe significantly correlated with the reduction in LV posterior wall thickness is consistent with the notion that the reduction in radial strain and strain rate in the continuous training group is a due to the reduction in thickness and not a reflection of contractility. Furthermore, with the reported increase in circumferential strain, an increase rather than a decrease in radial strain should be expected. The absence of increased radial strain possibly reflects a training-induced change in myocardial fibre orientation.

From these data, it is shown that both continuous and interval heavy-intensity training induce similar improvements in LV systolic and diastolic function in healthy overweight/obese women that can only be detected by novel TDI and 2DST echocardiography. Aerobic exercise enhances myocardial contractile function through several mechanisms including increased IGF-1 expression with subsequent activation of AKT leading to improvement in Ca^{2+} handling through phosphoilamban phosphorylation and disinhibition of sarcoplasmic reticulum Ca^{2+} ATPas pump (Gielen 2013). Furthermore, IGF-1 expression results in improved myocardial repair and function and the increase in the number of newly formed myocytes (Ellison 2012). It was also shown that exercise intensity is directly related to exercise-induced influence on cell length, myocardial relaxation and calcium decay, being more beneficial with high intensities (Gielen 2013). Additionally, exercise is a powerful regulator of endothelial nitric oxide synthase- (eNOS-) mediated release of nitric oxide (NO). The exercise-induced enhancement in Ca^{2+} handling and length-dependent increase in myocardial contraction is regulated by eNOS (Ellison 2012). Furthermore, aerobic exercise results in up-regulation of anti-oxidative enzymes and reduction in ROS release, as well as enhance mitochondrial function and reduces ROS generation from the mitochondria (Gielen 2013), all of which are mechanisms contributing to obesity cardiomyopathy as explained in the literature review chapter.

6.4.5 Conclusions

In conclusion, both interval and continuous heavy-intensity training induced favourable LV structural changes that differed in nature according to baseline LV size and morphology in each groups. Continuous training induced reverse remodelling of obesity-mediated concentric hypertrophy by reducing LV posterior wall thickness, mass and relative wall thickness. Interval training slightly increased LV wall thickness and mass, contributing to an early exercise-induced LV remodelling. Changes in wall thickness following aerobic training precedes diameter changes as both training types did not lead to any change in LVIDd, possibly due to the short duration of the exercise programme. With regards to function, both interval and continuous heavy-intensity training resulted in equal improvements in both systolic and diastolic function. These improvements were only detected by TDI and 2DST echocardiography as no change was observed in standard echocardiography. A significant increase in 2DST-derived global longitudinal SRs, systolic circumferential strain, circumferential SRe and SRa was

observed in both groups in addition to an increase in TDI-derived Em and Em/Am and a decrease in Am and MPI. These changes are most likely secondary to improvement in myocardial contractility as no changes in preload, afterload or resting heart rate were detected. Finally, global LV radial strain, SRs and SRe followed the changes in wall thickness, decreased in the continuous group and slightly increased in the interval group. This is believed to be secondary to changes in thickness rather than contractility. This study confirms that exercise alone, without dietary modification, is an effective measure of improving LV structure and function in healthy overweight and obese women, protecting against the development of obesity cardiomyopathy. Furthermore, this study suggests that interval training is not superior to continuous exercise in improving cardiac function when both are in the heavy-intensity domain and that no additional benefit is observed from the repetitive nature of interval exercise. Since both training types were matched for work, the session durations of continuous training were much shorter than interval training. This could offer overweight and obese individuals the option of training for shorter durations and obtain similar benefits as longer interval training sessions when time constraints is a hindrance to training.

6.4.6 Limitations and future work

This study includes a small number of participants, making it difficult to draw strong conclusions from it. Results from this study require validation through future studies including large numbers of participants. Before the training intervention, both groups included in this study were matched for age, BMI and cardio-respiratory fitness, but not for LV size and morphology and due to the significant differences between both groups in LV structure, it was impossible to compare the impact of both types of exercise on LV structure. Future studies are required comparing both types of exercise after matching participants for LV size, morphology and function. This study is observational and does not provide information on molecular mechanisms. Future longitudinal studies supported by cellular/molecular techniques are required. This study lacks a non-obese control group, as the aim was to compare the effects of both types of exercise on LV structure and function in obese women. Future studies including a non-obese control group are required in order to confirm the findings were exclusively attributed to training and not to other potential external factors. Finally, this study is a women-only study and does not account for other potentially influencing

factors such as age, gender, race and genetic factors. Large-scale studies including a mixture of age groups, genders and races are required.

Chapter 7 General discussion

The aim of this chapter is to tie together the key findings presented in the thesis, discuss their clinical and research implications as well as their implications on the community, highlight the potential limitations of each study and provide suggestions for future direction and research.

7.1 Summary of findings

This study was set out to address the following aims: (1) To explore the physiological relationship between LV size and morphology, and body size and composition in a population of healthy women. (2) To assess the independent influence of excess body fat, particularly visceral adiposity, on LV size, morphology and function in healthy mild-moderately obese women. (3) To investigate the LV systolic and diastolic functional alterations during and immediately following heavy-intensity exercise in healthy obese women. (4) To explore the LV structural and functional adaptations to heavy-intensity interval and continuous exercise training in healthy overweight/obese women. (4) To determine whether interval exercise training provides any additional benefit over continuous exercise training on LV adaptations to aerobic training in healthy overweight/obese women.

Chapter 4 explored the impact of body size and composition on LV structure and function in healthy women. The principal findings were that, LV size was related to body size in a non-linear fashion and that body composition determined the pattern of LV morphology. Increased muscle mass was accompanied by a parallel increase in LVM following an eccentric morphology, whereas increased fat mass, particularly visceral fat, caused LVM to increase at a slower rate and in a concentric morphological pattern. Furthermore, normalising LVM for BM or BSA using allometric scaling techniques, masked the influence of excess body fat on LV size, which was avoided by normalising to FFM. With regards to LV function, this study provided evidence of reduced both systolic and diastolic function in healthy overweight/moderately obese women, which appeared to be mediated exclusively by excess body fat, particularly visceral adipose tissue. There was no evidence suggesting a need to normalise measures of LV function to FFM. Finally, this study showed for the first time that excess epicardial adipose tissue is independently associated with reduced LV systolic

myocardial deformation, suggesting a possibility of a local mechanical influence of epicardial fat on LV systolic performance.

Chapter 5 compared the LV systolic and diastolic functional response to heavy-intensity exercise in healthy obese and non-obese women. The primary findings were that, obese women displayed higher SBP than non-obese women during exercise indicating a high risk of developing hypertension. Furthermore, despite having similar systolic and lower diastolic LV function at rest, obese women displayed higher LV systolic and diastolic function during and following heavy-intensity exercise compared to non-obese women. This is possibly a compensatory means of optimising adequate cardiac output for the perfusion of exercising muscles. However, obese women displayed evidence of delayed HRR post-exercise, which may reflect impaired vagal reactivation possibly secondary to insulin resistance. Finally, this study reports for the first time a post-exercise improvement in LV diastolic filling and myocardial deformation in non-obese women only. The absence of this manifestation in obese women may reflect a subtle exercise-induced cardiac fatigue.

Chapter 6 assessed the long-term LV structural and functional adaptations to heavy-intensity interval and continuous exercise training in overweight/moderately obese women. The principal findings were that both types of exercise resulted in favourable alterations in LV structure and improvements in both systolic and diastolic function. Additionally, there was no evidence to suggest that interval exercise provides additional benefits over continuous exercise when both types of exercise are matched for work and exercise intensity domain. Finally, this study shows that exercise intensity and total amount of work per session rather than session duration and work-rate determine the training-induced improvements in LV function.

7.2 Practical implications

This section will discuss the practical implications of the key findings of this thesis. These will be broken down into clinical, research and implications on obese women.

7.2.1 Clinical implications

Chapter 4 highlights the importance of normalising LV size to the right body size variable before comparisons between individuals is to be carried out, particularly when it involves overweight/obese subjects. This is of significant

clinical importance because of the detrimental impact of LV hypertrophy on cardiovascular morbidity and mortality (Levy et al., 1990). To date, LVM is typically normalised to either BSA, HT or $HT^{2.7}$ both in the clinical and research settings. The reported allometric exponents for HT relative to LVM have been disparate, and we have failed to detect a significant relationship between HT and LVM. Additionally, we have shown that scaling LVM to BSA, even allometrically, underestimates LVM in overweight and moderately obese women and masks the impact of excess body fat. This was avoided when LVM was scaled to FFM. Therefore, using FFM as a scaling variable provides an accurate interpretation of LV size and is more sensitive for the identification of LV hypertrophy in mild degrees of obesity. To date, cut-off values for LVM scaled to FFM have not yet been developed and large epidemiological studies are required for this purpose.

Chapter 5 draws the attention to the importance of exercise stress testing for the detection of subtle cardiovascular dysfunction not apparent at rest. Obese women were shown to have high SBP during exercise and delayed HRR following exercise, despite having normal HR and SBP at rest. Both these manifestations reflect underlying cardiovascular and metabolic abnormalities. Therefore, high risk individuals, notably obese subjects, should have regular exercise stress tests to allow the early detection of subclinical abnormalities in cardiovascular function and the early implementation of appropriate treatment and follow up.

This thesis also underscores the importance of using novel echocardiographic techniques in the assessment of LV function in obese individuals both in clinical and research settings. In Chapters 4, 5 and 6, TDI and 2DST echocardiography revealed systolic and diastolic functional abnormalities that were not detected by standard 2D and PWD echocardiography. This was particularly evident with LV systolic function. To date, EF remains the most widely used indicator of LV systolic performance in clinical setting due to its ease of measurement. Although the routine use of TDI and 2DST-echocardiography can be more time consuming than standard echocardiography, they can potentially detect subtle LV systolic dysfunction in apparently healthy obese individuals allowing for early interventional measures to be initiated and the potential avoidance of eventual cardiac failure.

7.2.2 Research implications

To date, studies exploring the long-term cardiac adaptations to exercise or functional response during exercise, have predominantly defined the exercise intensity as a percentage of HR_{max}, VO_{2max} or designed fixed WR exercise sessions (Ingul et al., 2010, Salvadori et al., 1999, Schrauwen-Hinderling et al., 2010). This method does not control for individual differences in metabolic activity. Indeed, participants exercising at fixed WRs or at particular percentages of HR_{max} or VO_{2max} may be exercising above or below their individual lactate threshold ie. at different training intensities relative to one another (Rossiter, 2011). Consequently, the physiological stimulus will be different between participants and hence, may explain the high discrepancy in LV response to exercise and long-term adaptation to exercise training between studies. In chapters 5 and 6, we have demonstrated that heavy-intensity exercise, a defined according to individual lactate thresholds, resulted in significant improvements in LV systolic function during exercise and after long-term training.

7.2.3 Implications on obese women

Obesity represents a major cardiovascular risk factor for women. Exercise training provides overweight and obese women with a means of protecting themselves against heart disease, and indeed improve their cardiac structure and function, particularly if they are struggling to reduce weight and/or maintain weight loss. The UK government recommends that adults exercise for ≥ 30 min moderate-intensity exercise on 5 days/week. However, the number of women who adhere to exercise is very small and was mainly attributed to lack of time and motivation (BHF, 2012). Recent evidence suggests that heavy-intensity interval exercise provides higher cardiac benefits than moderate-intensity continuous exercise (Wisloff et al., 2007). Additionally, we have demonstrated that heavy-intensity exercise, regardless of exercise type and session duration, provides significant improvements in LV systolic and diastolic function in obese women. Indeed, continuous exercise for significantly shorter session durations than interval exercise (approximately 13 – 25 min vs 20 – 40 min respectively) resulted in similar improvements in LV function. This was provided it fell within the heavy-intensity domain and resulted in equivalent total amount of work as an interval training session. Hence, this may address the issue of lack of adherence because of lack of motivation and/or time. Women who lack motivation may find interval training more enjoyable, whereas women who

lack time may find continuous exercise for shorter duration more convenient and practical.

7.3 Limitations and future work

The main limitation in this thesis is the small number of participants included in each study which makes it difficult to draw firm conclusions from these studies. Therefore, the reported findings require validation by studies on larger population samples. Moreover, Chapters 4 and 5 are cross-sectional studies and do not take into account individual differences in the duration of obesity. Therefore, they do not provide information on mechanisms, causes, trends and changes over time and effects. Future longitudinal studies are required to explore the influence of time and duration of obesity on the obesity-mediated LV structural and functional alterations both at rest and during exercise by frequent follow up assessments at different time points. Additionally, Chapter 5 assessed LV function at a single time point during heavy-intensity exercise. This does not provide information on the pattern of change in LV function throughout the exercise session. Continuing is required to assess LV function during heavy intensity exercise at multiple time points covering the beginning, middle and end of exercise. Furthermore, in chapter 6, both groups had significantly different baseline LV size and morphology which has made it impossible to compare between both types of exercise with regards to their impact on LV structure. Continuing work is required to compare the impact of work- and intensity-matched interval and continuous exercise training on LV structure after matching participants for LV size and morphology before training. Moreover, this work does not control for potentially relevant factors such as race and genetic factors as it involved women only.

There are a number of limitations related to the echocardiographic technique employed in this thesis. Firstly, this thesis included overweight and obese women, which poses an important limitation to echocardiography. Excess adipose tissue can compromise image quality which can potentially affect the analysis of data. Therefore, tissue harmonic imaging was used in order to improve image quality and images were optimised to maximise spatial and temporal resolution. Additionally, physical limitations have been encountered in Chapter 5 during the echocardiographic assessment during exercise. Exercise results in a significant amount of motion, both through the exercising muscles and faster breathing. This can affect image quality and result in insufficient visualisation of the LV walls. Furthermore, it can affect

the positioning of the echocardiographic probe on the chest was of the exercising participant, resulting in inadequate image planes. Finally, the serial acquisition of different image planes is time consuming and during exercise, echocardiographic assessment has to be performed in a narrow time-window, which also affects imaging quality. Future studies exploring the LV functional alterations during exercise overcome using cardiac MRI can overcome these limitations and validate our findings.

Finally, one of the principal limitations of this work is the difficulty to translate the concept of exercise intensity to the public. The definition exercise intensity according to lactate threshold and the calculation of appropriate exercise work-rates that would fall in the heavy-intensity domain require specialised equipment and the performance of a maximal cardio-pulmonary exercise test. Future studies are required to develop alternative methods allowing the easy and quick estimation of individual lactate thresholds and subsequent calculation of work-rates corresponding to the heavy-intensity domain in order for healthcare professionals to be able to prescribe exercise interventions for obese individuals.

7.4 Conclusion

In summary, excess visceral adipose tissue is associated with subclinical LV concentric hypertrophy and subtle LV systolic and diastolic dysfunction in otherwise healthy overweight/moderately obese women. Furthermore, allometric scaling of LVM for FFM allows the detection of LV hypertrophy in obese women, whereas normalising for BSA or BM underestimates of LV size in these women by overcorrecting for body size. Additionally, novel TDI and 2DST echocardiography are more sensitive than standard echocardiography in detecting subtle LV systolic and diastolic dysfunction in overweight/obese women. Heavy-intensity exercise induces beneficial LV structural and functional adaptations, both during exercise and following long-term training in overweight and obese women. Finally, interval training does not seem to provide any additional benefits over continuous training on LV structural and functional adaptations to exercise after both types of exercise were matched for total amount of work and intensity domain. However, further studies are required to explore the influence of obesity duration on LV structure and function and the pattern of change in LV function during heavy-intensity exercise.

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Appenix 1 Ethics Approval Letters

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Dr Karen Birch
Centre for Sports and Exercise Sciences
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Biological Sciences Faculty Research Ethics Committee
University of Leeds

25 March 2015

Dear Karen

Title of study: **The effect of (i) physical activity and (ii) continuous versus intermittent exercise training upon cardiovascular and cognitive function in obese women.**

Ethics reference: **BIOSCI 10-021**

I am pleased to inform you that the above research application has been reviewed by the Biological Sciences Faculty Research Ethics Committee and following receipt of the amendments requested, I can confirm a favourable ethical opinion on the basis described in the application form and supporting documentation as submitted at date of this letter.

The following documentation was considered:

Document	*Version*	*Date*
BioSci 10-021 response to prov opinion obesity study.doc	1	19/05/11
BIOSCI 10-021 Obesity ethics form final.doc	2	19/05/11
BIOSCI 10-021 Info sheet obesity final.doc	2	19/05/11
BIOSCI 10-021 Protocol obesity final.docx	1	03/05/11

Please notify the Committee if you intend to make any amendments to the original research as submitted at date of this approval. This includes recruitment methodology and all changes must be ethically approved prior to implementation.

Please note: You are expected to keep a record of all your approved documentation, as well as documents such as sample consent forms, and other documents relating to the study. This should be kept in your study file, which should be readily available for audit purposes. You will be given a two week notice period if your project is to be audited.

Yours sincerely

Jennifer Blaikie
Research Ethics Administrator
Research Support
On Behalf of Professor Eric Blair
Chair, BIOSCI Faculty Research Ethics Committee

CC: Faculty Research Office

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Biological Sciences Faculty Research Ethics Committee
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Dr Ali Khalil
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Biological Sciences Faculty Research Ethics Committee
University of Leeds

25 March 2015

Dear Dr Ali Khalil

Title of study **In-Exercise Assessment of Cardiac Structure and Function in Obese Subjects**
Ethics reference **BIOSCI 11-023**

I am pleased to inform you that the above application for ethical review has been reviewed by the Biological Sciences Faculty Research Ethics Committee and following receipt of your response to the Committee's initial comments, I can confirm a favourable ethical opinion on the basis of the information provided in the following documents:

Document	*Version*	*Date*
BIOSCI 11-023 Ethics response.doc	1	21/09/12
BIOSCI 11-023 In-Exercise_Ethical_Review_Form_V3_Ali.doc	2	21/09/12
BIOSCI 11-023 Participant_info_sheet_in-exercise_ali_final.doc	2	21/09/12
BIOSCI 11-023 recruitment email.doc	1	24/08/12
BIOSCI 11-023 recruitment email_overweight.doc	1	24/08/12
BIOSCI 11-023 in-exercise study poster.pub	1	24/08/12
BIOSCI 11-023 in-exercise study poster_overweight.pub	1	24/08/12

Please notify the committee if you intend to make any amendments to the original research as submitted at date of this approval, including changes to recruitment methodology. All changes must receive ethical approval prior to implementation. The amendment form is available at www.leeds.ac.uk/ethics.

Please note: You are expected to keep a record of all your approved documentation, as well as documents such as sample consent forms, and other documents relating to the study. This should be kept in your study file, which should be readily available for audit purposes. You will be given a two week notice period if your project is to be audited. There is a checklist listing examples of documents to be kept which is available at
http://researchsupport.leeds.ac.uk/index.php/academic_staff/good_practice/other_information_nhs_sites in the '*Other useful documentation*' section.

Yours sincerely

Jennifer Blaikie
Senior Research Ethics Administrator
Research & Innovation Service
On Behalf of Karen Birch
Chair, BIOSCI Faculty Research Ethics Committee

CC: Student supervisor(s)

Appendix 2 Informed Consent Forms

Version 2: 19/05/2011

INFORMED CONSENT FORM

The relationship between body size and cardiac structure and function

Please Initial

1. I confirm that I have read and understood the Participant Information Sheet dated 19/05/2011 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. _____

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. _____

3. I understand that data collected during the study, may be looked at by individuals from the University research team, collaborators on the research project and the University of Leeds for the purposes of research governance. All data will be anonymised with the exception of the recruitment questionnaires containing personal data. I give permission for these individuals to have access to my data. _____

4. I agree to take part in the above study _____

Participant's name..... Date ____ / ____ /_____

Signature

.....

Researcher's name.....Date ____ / ____ /_____

Signature

.....

Version 2: 21/09/2011

INFORMED CONSENT FORM

Please Initial

In-Exercise Assessment of Cardiac Structure and Function In Subjects with BMI > 30

1. I confirm that I have read and understood the Participant Information Sheet dated 21/09/2012 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. _____

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. _____

3. I understand that data collected during the study, may be looked at by individuals from the University research team, collaborators on the research project and the University of Leeds for the purposes of research governance. All data will be anonymised with the exception of the recruitment questionnaires containing personal data. I give permission for these individuals to have access to my data _____

4. I give permission to keep my details on file and be contacted for further studies _____

5. I agree to take part in the above study _____

Participant's name..... Date ____/____/_____

Signature .....

Researcher's name.....Date ____/____/_____

Signature .....

Version 2: 19/05/2011

INFORMED CONSENT FORM

Please Initial

The effect of (i) physical activity and (ii) continuous versus intermittent exercise training upon cardiovascular and cognitive function in obese women

1. I confirm that I have read and understood the Participant Information Sheet dated xx xxx xxxx (version x) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. _____

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. _____

3. I understand that data collected during the study, may be looked at by individuals from the University research team, collaborators on the research project and the University of Leeds for the purposes of research governance. All data will be anonymised with the exception of the recruitment questionnaires containing personal data. I give permission for these individuals to have access to my data. _____

4. I agree to take part in the above study _____

5. I give/do not give permission for my contact details to be kept securely on file for potential future studies (please delete as appropriate) _____

Participant's name..... Date ____ / ____ /_____

Signature

.....

Researcher's name.....Date ____ / ____ /_____

Signature

.....