Improvement of left ventricular function by lifestyle intervention in obesity: contributions of weight loss and reduced insulin resistance

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Abstract

Aims/hypothesis Weight excess and insulin resistance mediate the link between obesity and left ventricular dysfunction. We investigated the effect and mechanisms of lifestyle modification on left ventricular function changes in obese patients.

Methods Reduction of body weight and insulin resistance was sought using a behavioural intervention programme including dietary restrictions and exercise training in 261 patients (age 45 ± 13 years) with $\text{BMI} \geq 30 \text{ kg/m}^2$, no history of cardiac disease and a normal stress echocardiogram. Each patient underwent echocardiographic measurement of myocardial deformation and velocity at baseline and at 6 month follow-up.

Results Improvements in left ventricular systolic and diastolic function were demonstrated only in patients with significant reduction of weight and/or insulin resistance. Left ventricular improvement was less frequent in patients

with diabetes than in those without (52% vs 82% for strain, 50% vs 81% for strain rate and 59% vs 80% for peak early diastolic myocardial velocity). The independent predictors of improved left ventricular systolic function (increase in strain) were: weight reduction ($\beta=0.14$, $p<0.05$), decrease in the HOMA insulin resistance index ($\beta=0.20$, $p<0.005$) and absence of diabetes ($\beta=0.18$, $p<0.02$). A decrease in HbA_{1c} also predicted improvement of left ventricular diastolic function ($\beta=0.26$, $p<0.001$). There was a parallel increment in exercise capacity with intervention and increase in strain was independently correlated with increase in $\dot{V}\text{O}_2$ ($\beta=0.13$, $p<0.04$).

Conclusions/interpretation Effective lifestyle modifications in obese patients improve left ventricular systolic and diastolic function, but appear less effective with co-existing diabetes. The reversal of left ventricular function abnormalities is associated with reduction of both weight and insulin resistance, and is accompanied by an increase in cardiorespiratory fitness.

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Abbreviations

Em	Peak early diastolic velocity
HOMA-IR	HOMA index of insulin resistance
SR	Peak systolic strain rate
$\dot{V}\text{O}_2$	Peak oxygen consumption

Introduction

Obesity is now a worldwide epidemic [1], with more than one of three US American adults ranked as obese [2]. The

public health ramifications are considerable, as obesity is an established risk factor for the development of heart failure, with effects on cardiovascular morbidity and mortality rates independent of commonly associated co-morbidities, such as coronary artery disease, hypertension and diabetes mellitus [3]. Subclinical left ventricular dysfunction is a common finding in overweight patients [4, 5] and may progress over time to overt heart disease. As weight excess and insulin resistance are considered to mediate the link between obesity and cardiac function [5, 6], successful strategies for weight reduction and improvement in metabolic status could improve left ventricular performance. However, diabetes imposes an additional metabolic burden on the heart, which may modulate the effects of weight loss on left ventricular function.

The most effective weight-reducing approach is gastric bypass surgery, but this is reserved for selected, usually morbidly obese patients [7–10]. Lifestyle modifications (energy intake restriction and increased physical activity) are essential in the management of obesity and its consequences, with even modest weight reduction (5–10%) likely to promote favourable alterations in cardiometabolic risk [11, 12]. However, the benefits of these steps on left ventricular function are less well defined. Therefore, by following myocardial deformation to detect subclinical left ventricular dysfunction in overweight participants [5, 13], we sought: (1) to investigate the effect of a lifestyle intervention with reduced dietary intake and exercise training on left ventricular performance; and (2) to identify the factors associated with a beneficial effect on cardiac function.

Methods

Patient selection

We prospectively evaluated 261 obese men and women ($\text{BMI} \geq 30 \text{ kg/m}^2$) with cardiovascular risk factors, who were referred to university hospitals from general practice and specialist clinics for management of obesity. All participants underwent a medical evaluation comprising clinical history, routine blood analysis, lipid profile, a 75 g OGTT (in patients without known diabetes), electrocardiography and echocardiography. Patients with a history of CHD were excluded, as were those with abnormal stress electrocardiograms or echocardiograms, or with non-diagnostic stress tests to $<85\%$ predicted maximum heart rate. Other exclusion criteria included: any known heart disease (including a history or findings suggesting heart failure), thyroid and renal diseases, pregnancy and chronic alcohol consumption.

Diabetes mellitus was diagnosed according to the criteria recommended by the American Diabetes Association [14]. Patients on oral hypoglycaemic therapy were eligible for

recruitment, but those being treated with insulin were excluded. Hypertension was defined by antihypertensive treatment or documented blood pressure measurements $\geq 140 \text{ mmHg}$ systolic and/or $\geq 90 \text{ mmHg}$ diastolic on at least two occasions. The metabolic syndrome was recognised as recommended by the International Diabetes Federation [15]. Cardiovascular risk was calculated according to the Framingham risk score [16]. Among cardiovascular risk factors considered were age, sex, total cholesterol, HDL-cholesterol, blood pressure, smoking status and presence of diabetes.

All participants were informed of the purpose of the study and provided written informed consent. Investigations were in accordance with the Declaration of Helsinki as revised in 2000 and were approved by the institutional ethics committees.

Description of intervention

Participants attended the lifestyle intervention programme, which included dietary restrictions and increased physical activity for 6 months and was targeted to achieve an energy deficit of 14.6–29.3 MJ/week. Exercise training encompassed an individualised exercise programme with at least 30 min of moderate-intensity physical activity on most days (a minimum approximately 150 min per week) as recommended by the American College of Sports Medicine and the International Association for the Study of Obesity [17, 18]. This exercise regimen is believed to lead to burning of fat stores, which occurs after the first 20 min of exercise with preferential utilisation of glycogen. Dietary modification consisted of personal advice by a dietitian with a view to reducing daily energy intake to 3.3–6.3 MJ and with $<30\%$ of energy requirement provided by lipids. We sought to avoid changes to medication during the observation.

The study sample was divided into two groups according to compliance with lifestyle modifications: (1) participants with good adherence demonstrating an arbitrary weight loss $>5\%$ at the end of the intervention programme; and (2) those with poor adherence and unable to achieve a 5% decrease in body weight.

Clinical evaluation

Anthropometric assessment including height, body weight and both hip and waist circumference was carried out after an overnight fast. Brachial blood pressure was estimated using standard sphygmomanometry with the participant in the sitting position. Measurements were repeated three times after at least 5 min of rest and then averaged.

Biochemical assays

Blood samples were obtained between 08:00 and 09:00 hours after overnight fast and supine rest for 30 min, and before

taking hypoglycaemic and antihypertensive drugs, exercise testing or echocardiography. Serum glucose was measured by enzymatic assay (Dade Behring, Newark, DE, USA). Serum insulin was evaluated using a chemiluminescent enzyme immunoassay (Immulite 2000; Diagnostic Products, Los Angeles, CA, USA). The HOMA index of insulin resistance (HOMA-IR) was computed as previously reported [19]. A 75 g OGTT was performed in each participant without prior diagnosis of diabetes.

Body composition

Body fat percentage was evaluated by dual energy X-ray absorptiometry (Discovery-W; Hologic, Bedford, MA, USA).

Metabolic exercise testing

Exercise testing was carried out on a treadmill exerciser according to a protocol individualised to the exercise capacity of the patients. Measurements of peak oxygen consumption ($\dot{V}O_2$) were performed using breath-by-breath analyses of expired gas (V29C; Sensormedics, Yorba Linda, CA, USA; and QPLEX; Quinton Instruments, Seattle, WA, USA).

Echocardiography

Echocardiographic examinations were performed using standard systems (Vivid 7 and System Five; GE Medical Systems, Horten, Norway) equipped with phased array 2.5 MHz multifrequency transducers.

Conventional echocardiography Left ventricular and left atrial dimensions and wall thicknesses were measured according to standard recommendations [20]. Left ventricular mass was determined from the modified American Society of Echocardiography cube formula and normalised for height to the power of 2.7 to achieve the left ventricular mass index [21]. A modified Simpson's biplane method was used to calculate left ventricular ejection fraction.

Pulsed wave Doppler recordings of the left ventricular inflow were obtained from the apical four-chamber view with the sample volume placed between the tips of the mitral leaflets. The peak early and late diastolic flow velocities, the ratio of peak early and late diastolic flow velocities, and the deceleration time of early diastolic flow were evaluated.

Tissue Doppler imaging To assess left ventricular longitudinal function, real-time colour tissue Doppler myocardial imaging data were acquired in the three apical views. The narrowest possible image sector angle and the optimal depth of imaging were used to achieve the maximal frame rate. Pulse repetition frequency was adjusted at the lowest level without aliasing. The sampled region was oriented as

parallel as possible to the myocardial segment of interest to ensure the imaging angle did not exceed 20°. The region of interest was continuously positioned by manual tracking in the mid-myocardial layer of each segment during the heart cycle. Digital data were stored in a cine-loop format, transferred to a dedicated workstation (Echopac; GE Medical Systems) and subsequently analysed off-line.

Myocardial velocities Regional myocardial velocity curves were extracted from colour Doppler data obtained in the basal segments of the interventricular septum in order to assess peak systolic velocity and peak early diastolic velocity (Em). Pulsed-wave tissue Doppler was recorded in the septal mitral annulus. The ratio of mitral inflow early diastolic velocity to the mitral annular Em was computed as an approximation of left ventricular filling pressure [22].

Myocardial deformation Left ventricular myocardial deformation curves were derived from the apical, mid and basal segments of each left ventricular wall. Strain-rate was evaluated from the tissue velocity gradient over a computation length of 12 mm. Strain rate profiles were then integrated over time to obtain the natural strain curves using end-diastole defined to occur at the R-peak of ECG as the reference point. The analysis of left ventricular deformation curves included peak strain, identified as the greatest negative value on the strain curve, and peak systolic strain rate (SR). All strain, strain rate and myocardial velocity profiles were averaged over three consecutive heart cycles and patient results were expressed as the average values from all segments.

All echocardiograms were obtained and analysed by readers blinded to patients' clinical data.

Feasibility No participants were excluded due to poor imaging quality. Despite great care during acquisition, 7% of all left ventricular segments were disqualified from further analysis due to unreliable interpretation of myocardial velocity and deformation profiles resulting from artefacts, poor signal:noise ratio or unfavourable angle of insonation. The reproducibility of tissue Doppler measurements was estimated in 15 randomly selected participants. The intra- and inter-observer variability was $1.6 \pm 1.2\%$ and $1.8 \pm 1.2\%$ for strain, 0.1 ± 0.1 and $0.1 \pm 0.1 \text{ s}^{-1}$ for SR, and 0.2 ± 0.8 and $0.3 \pm 0.7 \text{ cm/s}$ for myocardial velocities, respectively.

Statistical analysis

Data are presented as mean $\pm$ SD; skewed variables were log-transformed. Intergroup comparisons were performed by an unpaired two-sided Student's *t* test or, with more than two groups included, by one-way ANOVA with Scheffé's post hoc test for continuous variables and by χ^2 for categorical

variables. Homogeneity of variances was evaluated by the Levene test. Longitudinal analyses were carried out using a repeated-measures two-way ANOVA with planned comparisons by the linear contrasts method. Associations between variables were studied using Pearson's correlation coefficient and stepwise multiple regression analysis. A receiver operator characteristic analysis was used to examine the ability of particular variables to predict left ventricular function improvement. Differences in the area under the receiver operator characteristic curves were analysed using the Z test [23]. Improvement of left ventricular function was defined in analyses by an increase in each variable (strain, SR and Em). Calculations were carried out with standard statistical software (Statistica for Windows 7; StatSoft, Tulsa, OK, USA). A value of $p < 0.05$ was accepted as statistically significant.

Results

Patient characteristics

The baseline characteristics are representative of persons enrolling in our weight loss programmes, i.e. middle-aged (45 ± 13 years) and predominantly female sex (64%). Post-menopausal status was established in 50 of the women participants (30%). Hypertension (36%), metabolic syndrome (62%) and type 2 diabetes mellitus (59%) were frequent, as were treatments for hypertension (ACE inhibitors/angiotensin receptor blockers 30%, beta-blockers 4%, calcium channel antagonists 12%, diuretics 29%) and diabetes (biguanides 63%, sulfonylureas 26%, no thiazolidinediones). The duration of follow-up was similar in the adherent and non-adherent groups (6.0 ± 1.7 vs 6.1 ± 1.6 months, $p = 0.81$).

The adherent patients were younger, more commonly women and less likely to have diabetes, and had lower baseline insulin, glucose, HOMA-IR, HbA_{1c}, waist circumference and WHR, and higher exercise capacity and Em than their peers from the poor adherence group (Tables 1 and 2). The 10-year risk of coronary heart disease (assessed by Framingham scoring) was 1% in women and 6% in men, and similar in both groups.

Effect of the lifestyle modifications

Participants with good adherence showed a significant decrease in weight and adiposity. They also experienced improvements in insulin resistance, lipid profile, cardiorespiratory fitness and left ventricular systolic and diastolic function, as well as reductions of left ventricular mass index at the end of the follow-up. The intervention caused no changes in clinical, laboratory and echocardiographic variables in the non-adherent group (Tables 1 and 2). Table 3 compares the changes in metabolic and imaging

variables in groups with baseline diabetes mellitus, hypertension or both. There was no difference in any variable between hypertension and non-hypertension patients, but important differences were seen between groups with or without diabetes.

Categorical improvements in strain, SR and Em with the lifestyle intervention were demonstrated in 82%, 81% and 80% of patients without diabetes respectively, compared with 52%, 50% and 59% of patients with diabetes, respectively ($p < 0.001$ for all).

Correlates of alterations in left ventricular function

The correlates of changes in left ventricular function following the lifestyle modifications in patients who adhered to the intervention are presented in Table 4. Changes in systolic function were independently associated with baseline systolic performance and metabolic alterations (Δ HOMA-IR, Δ BMI, co-existence of diabetes); diastolic changes were independently associated with baseline diastolic performance and metabolic alterations (Δ BMI, Δ HbA_{1c}). Comparison of the AUCs in the prediction of left ventricular function improvement revealed equivalent values of Δ HOMA-IR and Δ BMI for systolic and diastolic variables (Fig. 1a–f). Among other factors, only Δ HbA_{1c} emerged as a significant predictor of left ventricular diastolic improvement (Δ Em) (AUC=0.69, SE=0.058, $p < 0.001$).

Change in strain was an independent correlate of $\Delta \dot{V}O_2$ even after adjustment for other variables including age, presence of diabetes, changes in BMI, HOMA-IR, left ventricular mass index, blood pressure and pharmacotherapy ($\beta = 0.13$, $p < 0.04$).

Influence of weight loss and insulin resistance reduction on left ventricular function and cardiorespiratory fitness improvement

The study population was re-classified on the basis of pre-defined cut-points of 5% decrease in body weight (used for the initial identification of adherence to the intervention) and 20% decrease in HOMA-IR to create the following four groups: (1) improvement in body weight and insulin resistance (BMI+IR+, $n = 79$); (2) improvement in body weight alone (BMI+IR−, $n = 45$); (3) improvement in insulin resistance alone (BMI−IR+, $n = 43$); and (4) no improvement in either (BMI−IR−, $n = 94$). Average weight change ranged from a reduction of 14 ± 8 kg in the BMI+IR+ group to an increase of 2 ± 10 kg in the BMI−IR− group. HOMA-IR change varied from 43% less to 41% more.

Each group with improvement in at least one of the two variables (i.e. BMI+IR+, BMI−IR+, BMI+IR−) demonstrated improvements in left ventricular systolic (Δ strain) and diastolic (Δ Em) functions. The cumulative effect of

Table 1 Demographic data, and baseline and follow-up clinical characteristics of the study group

Variables	Adherent (<i>n</i> =124)			Non-adherent (<i>n</i> =137)			<i>p</i> value, adherent vs non-adherent	
	Baseline	Follow-up	<i>p</i> value	Baseline	Follow-up	<i>p</i> value	Baseline	Follow-up
Demographic and clinical features								
Age (years)	41±13	–		49±12	–		0.0001	–
Sex (% male)	24	–		47	–		0.001	–
Diabetes (%)	36	–		80	–		0.0001	–
Hypertension (%)	35			36			0.81	
Smoking (%)	17			25			0.13	
Body weight (kg)	102±18	90±17	0.0001	100±19	101±20	0.06	0.42	0.0001
BMI (kg/m ²)	36.4±5.7	31.2±5.4	0.0001	35.1±5.5	35.5±6.0	0.07	0.07	0.0001
Body fat (%)	39.5±10.1	37.3±9.5	0.0001	39.0±8.2	39.4±8.7	0.24	0.71	0.23
Waist circumference (cm)	107±12	101±10	0.0001	111±14	112±14	0.10	0.04	0.0001
WHR	0.92±0.09	0.89±0.09	0.01	0.95±0.10	0.94±0.10	0.27	0.03	0.0001
Systolic BP (mmHg)	127±13	127±17	0.82	129±15	130±15	0.4	0.35	0.38
Diastolic BP (mmHg)	81±9	80±9	0.11	81±9	81±8	0.64	0.71	0.43
Laboratory findings								
Fasting insulin (pmol/l)	103±48	79±57	0.0001	126±99	121±86	0.60	0.02	0.0001
Fasting glucose (mmol/l)	6.0±2.1	6.0±2.7	0.69	7.8±3.0	8.2±3.3	0.10	0.0001	0.0001
HOMA-IR	4.1±2.7	3.4±2.8	0.04	6.1±5.0	6.4±5.0	0.45	0.0001	0.0001
HbA _{1c} (%)	6.5±1.3	6.5±1.4	0.53	7.4±1.6	7.5±1.4	0.60	0.0001	0.0001
LDL (mmol/l)	3.0±0.9	2.8±1.0	0.03	2.9±0.9	2.9±1.0	0.77	0.12	0.62
HDL (mmol/l)	1.3±0.3	1.4±0.4	0.001	1.3±0.3	1.3±0.4	0.14	0.77	0.52
Triacylglycerol (mmol/l)	1.7±1.0	1.8±2.9	0.66	2.0±2.2	2.1±2.0	0.40	0.10	0.49
Exercise capacity								
$\dot{V}O_2$ (ml kg ⁻¹ min ⁻¹)	24.8±9.0	27.1±9.7	0.001	22.4±7.3	22.8±7.9	0.19	0.03	0.001

Unless otherwise indicated values are mean±SD

reduced weight and insulin resistance exceeded that of a change in only one variable, evidenced by statistical differences in Δ strain and Δ Em between the BMI+IR+ group and the BMI-IR+ or BMI+IR- group.

The enhancement of left ventricular performance seen in patients with BMI and HOMA-IR improvements was accompanied by an increase in peak ventilatory exercise capacity, which was significantly higher in patients from the BMI+IR+ and BMI+IR- groups as compared with the BMI-IR- group (Fig. 2a–e).

Cardiac response to lifestyle modification

Based on changes in body weight, insulin resistance and left ventricular function, we identified two extremes in the cardiac response to lifestyle modification. Cardiac responders included participants from the BMI+IR+, BMI+IR- and BMI-IR+ groups (with weight reduction >5% and/or HOMA-IR decrease >20%), who exhibited improvement in strain. Non-responders were individuals from the BMI-IR- group and showed no improvement in strain. Cardiac responders were characterised by younger age, lower preva-

lence of diabetes and male sex, and lower baseline WHR, strain and SR than non-responders (Table 5).

Discussion

The main clinical findings of the present study are that improved left ventricular systolic and diastolic function in obese patients is observed in connection with effective lifestyle modifications (i.e. those associated with weight loss and reduced insulin resistance) and less likely in patients with co-existing diabetes. The possibility of left ventricular function improvements during lifestyle intervention is higher in participants who are younger, of female sex, without diabetes and have less extensive visceral fat deposition and more severe baseline cardiac function impairment.

Mechanisms of cardiac function improvement during lifestyle intervention

Lifestyle intervention may improve cardiac structural and functional pathologies through a variety of mechanisms [4–6,

Table 2 Baseline and follow-up values of echocardiographic characteristics of the study group

Echocardiographic characteristics	Adherent (<i>n</i> =124)		<i>p</i> value	Non-adherent (<i>n</i> =137)		<i>p</i> value	<i>p</i> value, adherent vs non-adherent	
	Baseline	Follow-up		Baseline	Follow-up		Baseline	Follow-up
LV end-diastolic dimension (mm)	50.3±4.8	49.9±4.6	0.20	49.3±5.4	48.9±5.5	0.29	0.12	0.13
LV mass index (g/m ^{2.7})	49.8±12.2	44.8±9.6	0.001	48.9±10.6	48.6±11.8	0.82	0.34	0.35
LV ejection fraction (%)	64.8±5.5	65.3±7.4	0.33	63.6±5.5	63.7±5.9	0.51	0.30	0.19
Left atrial dimension (mm)	39.6±2.9	39.4±3.1	0.44	39.3±3.1	38.9±2.0	0.28	0.69	0.47
E/E'	8.2±2.1	8.0±1.9	0.71	8.8±2.5	8.5±2.0	0.24	0.32	0.25
E/A	1.2±0.3	1.2±0.3	0.45	1.2±0.4	1.2±0.3	0.66	0.68	0.96
IVRT (ms)	100±15	98±13	0.24	101±16	101±15	0.95	0.72	0.41
Sm (cm/s)	5.7±1.5	6.0±1.4	0.03	5.5±1.7	5.7±1.6	0.12	0.29	0.28
Em (cm/s)	6.5±2.1	8.0±2.5	0.0001	5.8±2.1	6.1±1.8	0.11	0.01	0.0001
Strain (%)	18.8±2.9	21.0±2.8	0.0001	19.5±3.6	19.8±3.5	0.32	0.07	0.01
SR (1/s)	1.51±0.28	1.65±0.34	0.0001	1.47±0.32	1.47±0.29	0.88	0.19	0.0001

Values are mean±SD

A, peak late diastolic mitral flow velocity; E, peak early diastolic mitral flow velocity; E', peak early diastolic mitral annular velocity; IVRT, isovolumic relaxation time; LV, left ventricular; Sm, peak systolic velocity

Table 3 Change of metabolic and imaging variables in groups with baseline diabetes mellitus, hypertension or both

Follow-up change	DM−		DM+		<i>p</i> value (HT+ vs HT−)	<i>p</i> value (HT− vs DM−)	<i>p</i> value (HT+ vs HT−)	<i>p</i> value (DM−HT− vs DM+HT+)	<i>p</i> value (HT+DM− vs DM+)	<i>p</i> value (DM+HT+ vs HT−)
	HT− (<i>n</i> =82)	HT+ (<i>n</i> =25)	HT− (<i>n</i> =84)	HT+ (<i>n</i> =70)						
BMI (kg/m ²)	−3.5±3.8	−4.4±3.1	−0.3±4.1	−0.7±1.5	0.75	0.0001	0.0001	0.0001	0.0001	0.72
BF (%)	−1.84±1.29	−3.03±2.29	−0.17±3.34	−0.57±3.38	0.21	0.001	0.001	0.001	0.001	0.44
Waist (cm)	−2.5±5.2	−2.7±4.2	−0.7±5.7	−0.9±3.5	0.40	0.001	0.38	0.001	0.89	0.10
WHR	−0.02±0.07	−0.02±0.05	−0.021±0.04	−0.01±0.02	0.20	0.06	0.37	0.03	0.77	0.27
HOMA-IR	−0.82±2.27	−1.08±1.26	0.10±4.21	0.50±5.97	0.81	0.02	0.01	0.001	0.01	0.80
I/O ₂ (ml kg ^{−1} min ^{−1})	3.32±5.38	3.61±3.48	0.54±3.66	0.35±2.96	0.84	0.002	0.02	0.001	0.01	0.76
Sm (m/s)	0.14±1.19	0.05±1.52	0.94±1.67	0.32±1.29	0.14	0.27	0.13	0.97	0.24	0.29
Em (cm/s)	1.17±1.82	1.45±1.72	0.65±1.55	0.30±1.69	0.20	0.21	0.003	0.05	0.004	0.20
Strain (%)	2.62±2.83	2.08±3.29	0.84±2.86	0.13±3.60	0.30	0.0001	0.003	0.0001	0.0004	0.34
SR (1/s)	0.21±0.32	0.08±0.54	0.01±0.27	−0.01±0.30	0.86	0.0001	0.03	0.0001	0.0004	0.11

Note the lack of difference between hypertension and non-hypertension patients in groups with and without diabetes

BF, body fat; DM, diabetes mellitus; HT, hypertension; Sm, peak systolic velocity;

Table 4 Significant independent correlates of changes in left ventricular systolic and diastolic function indices in obese patients with good adherence to the intervention

Variables	R^2	β	p value
Δ Strain	0.47		
Baseline strain		−0.50	0.0001
Δ HOMA		0.20	0.005
Diabetes		−0.18	0.02
Δ BMI		0.14	0.05
Δ LVMi		0.10	0.15
Δ SR	0.51		
Baseline SR		−0.61	0.0001
Diabetes		−0.47	0.0001
Δ BMI		0.14	0.04
Δ HOMA		0.18	0.01
Δ Em	0.32		
Baseline Em		−0.52	0.0001
Δ BMI		0.27	0.001
Δ HbA _{1c}		0.26	0.001
Diabetes		−0.11	0.21

In the multivariable forward stepwise regression models, the following variables were tested: age, sex, use of medications, presence of diabetes and hypertension, baseline values and follow-up changes (Δ) in BMI, HOMA-IR, HbA_{1c}, left ventricular mass index (LVMi), blood pressure, waist circumference, WHR and body fat percentage, as well as baseline values of particular left ventricular function variables (i.e. strain, SR and Em)

24]. Reduced energy intake and regular exercise training lead to weight loss and reduced insulin resistance. Weight and adipose tissue loss may contribute to improvement in left ventricular function by decreasing volume overload and cardiac output, attenuating cardioinhibitory cytokine activation and inhibiting neurohormonal disturbances involving the sympathetic nervous system, angiotensin II, leptin, adiponectin and hyperinsulinaemia. The intervention may alter cardiac structural changes including myocyte hypertrophy, interstitial fibrosis, sodium retention and disturbances in myocardial metabolism, e.g. AMP-activated protein kinase [9, 10, 25–27]. Finally, repeated exercise stimulates skeletal muscle glucose uptake and metabolism, thereby improving insulin resistance independently of weight reduction [28].

Clinical effects of improved myocardial function

There is experimental and clinical evidence for the salutary effect of weight loss on cardiac morphology and function [26, 29–35]. Irrespective of the means of weight loss (surgical, pharmacological, dietary or physical training) [8–10, 25, 33, 34], small clinical studies have shown left ventricular mass reduction, improvement in left ventricular diastolic function

and a minor increase in left ventricular systolic function [7, 10, 36]. The amelioration of cardiovascular disturbances has been related to the amount of weight loss, with other factors potentially contributing to the observed cardiac benefit receiving little or no attention [9, 37].

The present study confirms the favourable effect of lifestyle intervention-induced weight loss and insulin resistance reduction on left ventricular systolic and diastolic function. In participants with good adherence to the dietary and exercise intervention programme, moderate weight reduction and metabolic improvement were observed, as well as favourable alterations in left ventricular mass, plasma lipid profile and cardiorespiratory fitness. In the group without significant weight loss, patients whose insulin resistance improved during the intervention also exhibited left ventricular function benefits. Thus, improvements in left ventricular systolic and diastolic function were associated with weight reduction and decline in insulin resistance. The additive beneficial effect of these two components, as shown in patients from the BMI+IR+ group, supports the notion of their complementary contribution.

Our data suggest that concurrent diabetes diminishes the likelihood of left ventricular function restoration in obese individuals. The reason for this is unclear. However, of all obese participants, those with diabetes mellitus had a greater metabolic and haemodynamic burden (e.g. higher baseline insulin, glucose, HOMA-IR and blood pressure), a greater deposition of visceral fat (a source of biologically active compounds influencing heart muscle) and higher HbA_{1c} (suboptimal glycaemic control is associated with cardiac dysfunction in diabetes). Effective hypoglycaemic treatment might be an important part of successful lifestyle modification in obese patients with diabetes, a notion possibly supported by the finding that a reduction in HbA_{1c} was independently associated with favourable changes in left ventricular diastolic function.

Left ventricular function improvement was clearly dependent on baseline myocardial performance, being more pronounced in patients with greater left ventricular function abnormalities, consistent with prior observations [7]. However, this finding might not apply to patients with overt impairment of left ventricular function, who may not demonstrate a proportionate degree of left ventricular recovery.

Response to the intervention

Left ventricular improvement was shown only in patients with a significant decrease in body weight and/or insulin resistance through the intervention programme, both paralleled by increment in exercise capacity. The participants who responded positively to the lifestyle modifications had a different baseline demographic and clinical profile to the non-responders, being younger and more likely to be of

Fig. 1 Receiver operator characteristic curves of the decrease in body weight (Δ BMI) (**a**, **c**, **e**) and insulin resistance (Δ HOMA) (**b**, **d**, **f**) in predicting left ventricular function improvement in obese participants

with good adherence to the intervention. Graphs show curves for strain (**a**, **b**), SR (**c**, **d**) and Em (**e**, **f**). AUC: **a** 0.71 ± 0.058 ; **b** 0.76 ± 0.056 ; **c** 0.69 ± 0.052 ; **d** 0.80 ± 0.048 ; **e** 0.72 ± 0.061 ; and **f** 0.73 ± 0.053

female sex and to have diabetes, lower visceral fat content and more depressed left ventricular function. These findings may help identify the patients who would be most likely to benefit from this type of lifestyle intervention.

Limitations

There are several important limitations to our study. First, we have followed myocardial functional indices rather than

Fig. 2 Changes in BMI (a), HOMA-IR (b), strain (c), Em (d) and $\dot{V}O_2$ (e) in obese patients according to weight reduction and improvement in insulin resistance. Values are follow-up change expressed as per cent of baseline (mean±SD). * p <0.05 vs BMI+IR+; ** p <0.01 vs BMI+IR+; *** p <0.001 vs BMI+IR+; † p <0.001 vs

BMI+IR-; ‡ p <0.001 vs BMI-IR+; § p <0.01 vs BMI-IR-; ¶ p <0.05 vs BMI+IR-. BMI+, weight reduction >5%; BMI-, no weight reduction >5%; IR+, decrease in insulin resistance >20%; IR-, no reduction in insulin resistance >20%

markers of myocardial structure (e.g. calibrated integrated backscatter, cardiac magnetic resonance), which might demonstrate interstitial abnormalities. Second, we anticipated changes in visceral adiposity but do not have imaging

evidence to support this. Third, although no changes to prescribed medications were planned, it is difficult to track all doses over the study interval and this requirement may have not been fulfilled in each case. Fourth, as the goal of

Table 5 Baseline demographic, clinical and echocardiographic characteristics of cardiac function responders to the lifestyle modifications

Variables	Responders ($n=130$)	Non-responders ($n=55$)	p value
Age (years)	42±13	49±12	0.001
Sex (% male)	24	55	0.0001
Diabetes mellitus (%)	40	82	0.001
HOMA-IR	5.1±4.6	4.4±3.3	0.31
Waist circumference (cm)	107±13	111±15	0.08
WHR	0.92±0.09	0.96±0.10	0.01
BMI (kg/m ²)	36.3±5.2	35.0±6.2	0.17
Body fat (%)	39.4±8.9	37.6±8.3	0.32
Systolic BP (mmHg)	128±15	128±16	0.96
Diastolic BP (mmHg)	82±9	81±10	0.59
$\dot{V}O_2$ (ml kg ⁻¹ min ⁻¹)	23.3±8.7	22.9±8.0	0.79
LV mass index (g/m ^{2.7})	50.0±11.5	47.2±11.0	0.23
Em (cm/s)	6.4±2.3	5.9±2.1	0.10
Strain (%)	18.3±2.7	20.9±3.0	0.0001
SR (1/s)	1.45±0.28	1.60±0.37	0.002

Unless otherwise indicated, values are mean±SD

Non-responders were participants without weight reduction >5% and/or insulin resistance decrease >20%, and without improvement in strain

Responders were participants with weight reduction >5% and/or insulin resistance decrease >20%, and improvement in strain

the study was to understand the links between weight loss and cardiac function, we used a no-weight-loss group as a frame of reference. Unfortunately, weight loss was lower in patients with diabetes than in those without, and the lack of a formal control group limits the ability to exclude confounding due to other changes (e.g. increased muscle mass), although given the lack of change in body composition, we believe this to be improbable. Finally, our study sample was relatively young, predominantly female and white, which limits extrapolation of our findings to groups with different age, ethnic and sex profiles.

Conclusions

Myocardial function may improve after reduction in body weight and insulin resistance following lifestyle modification in patients with obesity. For these changes to occur, however, programme adherence is required. The cardiac benefit of intentional weight reduction in early-stage disease contrasts with the ‘obesity paradox’ of late-stage heart failure, where obesity appears to favourably affect prognosis.

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