ORIGINAL ARTICLE

The relative contribution of metabolic and structural abnormalities to diastolic dysfunction in obesity

JJ Rayner, R Banerjee, CJ Holloway, AJM Lewis, MA Peterzan, JM Francis, S Neubauer and OJ Rider

BACKGROUND: Obesity causes diastolic dysfunction, and is one of the leading causes of heart failure with preserved ejection fraction. Myocardial relaxation is determined by both active metabolic processes such as impaired energetic status and steatosis, as well as intrinsic myocardial remodelling. However, the relative contribution of each to diastolic dysfunction in obesity is currently unknown.

METHODS: Eighty adult subjects (48 male) with no cardiovascular risk factors across a wide range of body mass indices (18.4–53.0 kg m^{-2}) underwent magnetic resonance imaging for abdominal visceral fat, left ventricular geometry (LV mass:volume ratio) and diastolic function (peak diastolic strain rate), and magnetic resonance spectroscopy for PCr/ATP and myocardial triglyceride content.

RESULTS: Increasing visceral obesity was related to diastolic dysfunction (peak diastolic strain rate, $r = -0.46$, $P = 0.001$). Myocardial triglyceride content ($\beta = -0.2$, $P = 0.008$), PCr/ATP ($\beta = -0.22$, $P = 0.04$) and LV mass:volume ratio ($\beta = -0.61$, $P = 0.04$) all independently predicted peak diastolic strain rate (model R^2 0.36, $P < 0.001$). Moderated multiple regression confirmed the full mediating roles of PCr/ATP, myocardial triglyceride content and LV mass:volume ratio in the relationship between visceral fat and peak diastolic strain rate. Of the negative effect of visceral fat on diastolic function, 40% was explained by increased myocardial triglycerides, 39% by reduced PCr/ATP and 21% by LV concentric remodelling.

CONCLUSIONS: Myocardial energetics and steatosis are more important in determining LV diastolic function than concentric hypertrophy, accounting for more of the negative effect of obesity on diastolic function than LV geometric remodelling. Targeting these metabolic processes is an attractive strategy to treat diastolic dysfunction in obesity.

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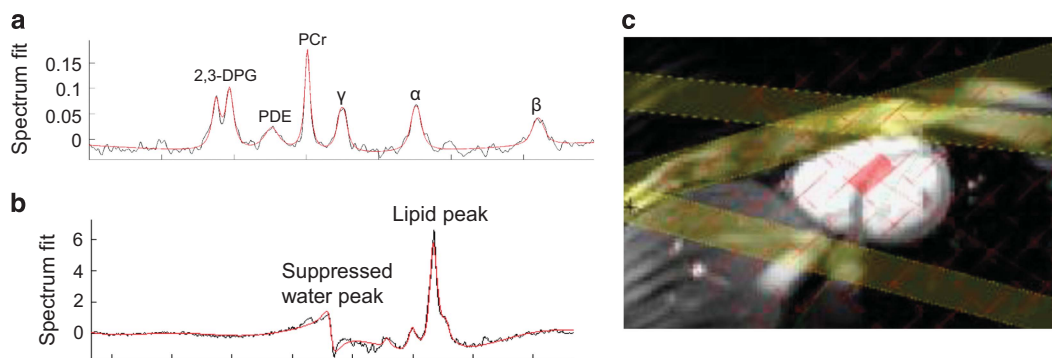
INTRODUCTION

It is now well established that obesity is intrinsically linked with the development of heart failure,[1,2] a condition with profound morbidity and mortality. The threatened global pandemic of obesity is likely to have a substantial impact on the incidence of heart failure. As the two conditions now frequently co-exist, the management of heart failure in the context of obesity is becoming a significant clinical concern.

Around 50% of patients presenting with new heart failure have normal systolic function, but rather pronounced diastolic impairment as the cause of their symptoms.[3] This is important, as although linked with heart failure with reduced ejection fraction at a population level, most reports indicate that obesity itself is not usually associated with systolic dysfunction, at least when measured with standard clinical parameters such as ejection fraction.[4,5] Haemodynamic studies have shown that left ventricular end-diastolic pressure may be elevated at rest in obesity and frequently increases significantly with exercise.[6,7] Regardless of the technique used, non-invasive imaging studies have also consistently shown that, even without co-morbidities such as hypertension or diabetes, impairment of left ventricular diastolic function occurs in all classes of obesity,[8–11] and almost all obesity metrics correlate with progressive diastolic impairment.[9,12,13] As a result, it is now clear that obesity contributes to diastolic dysfunction, and has been demonstrated to be one of the leading causes of heart failure with preserved ejection fraction (HFpEF).[3,14]

Despite the disease prevalence, clinical trials in HFpEF have produced neutral results and treatments are largely directed towards associated conditions and symptoms rather than towards improving diastolic function. As a result, understanding the mechanisms by which obesity causes diastolic dysfunction is increasingly important and may yield additional therapeutic strategies to treat this major health burden. Myocardial relaxation involves both active processes such as calcium handling and myocardial energetics,[15] and intrinsic physical properties of the LV (predominantly determined by chamber geometry and concentric hypertrophic remodelling[16]). In addition, myocardial steatosis and subsequent lipotoxicity are becoming increasingly recognised in human obesity and have been shown to be related to diastolic dysfunction.[17]

However, mitochondrial dysfunction, lipotoxicity and LV concentric remodelling are not completely distinct effects, and all three have been linked to an over-utilisation of fatty acids within the obese, insulin-resistant myocardium.[18] Despite this, the progression of these pathways and the relative contribution of each to diastolic dysfunction in obesity are unclear, but are an important consideration when considering future targeted therapy.

Here, we have used state-of-the-art magnetic resonance imaging and multinuclear spectroscopy to investigate the relationship between, and relative contributions of, myocardial energetics, myocardial steatosis and concentric LV remodelling to diastolic dysfunction in a population with increasing adiposity.

Oxford Centre for Clinical Magnetic Resonance Research, University of Oxford, Oxford, UK. Correspondence: Professor OJ Rider, Department of Cardiovascular Medicine Radcliffe Division of Medicine, John Radcliffe Hospital, Oxford OX3 9DU, UK.
E-mail oliver.rider@gmail.com

Figure 1. Representative myocardial spectra demonstrating ^{31}P spectroscopy (**a**); 2,3-DPG, 2,3-diphosphoglycerate; PDE, phosphodiesterase; PCr, phosphocreatine; γ β α, gamma, beta and alpha phosphate groups of ATP), ^{1}H spectroscopy (**b**) and the position of the basal septal voxel (**c**).

MATERIALS AND METHODS

Ethics and study cohort
The study protocol was approved by the National Research Ethics Service (NRES ref 09/H0505/97, 10/H0604/95). Eighty adult subjects (32 female, 48 male) across a body mass index (BMI) range of 18.4–53.0 kg m^{-2} were recruited to the study from the Oxfordshire population. Written informed consent was obtained from all participants. Subjects were asked to fast overnight prior to the study day.

Inclusion criteria
Volunteers were excluded if they were prescribed any cardiac medication (including antihypertensive or lipid-lowering agents) or if they had any smoking history, diabetes mellitus (fasting glucose > 7.0 mmol l^{-1}), hyperlipidaemia (cholesterol > 6.5 mmol l^{-1}), hypertension (systolic > 140 mm Hg; diastolic BP > 90 mm Hg), obstructive sleep apnoea or an abnormal electrocardiogram. Patients with heart failure or valvular disease, or with any contraindication to MR scanning, were also excluded.

Anthropometric and biochemical measurements
Height and weight were measured using digital scales (Seca, Birmingham, UK) and used to calculate BMI. Fasting venous blood was drawn and sent for biochemical analysis of total cholesterol, serum triglyceride content, insulin and glucose. Blood analysis was performed by the Oxford University Hospitals clinical grade biochemistry laboratories. Blood pressure was measured as an average of three supine measures (DINAMAP-1846-SX, Critikon Corp).

Adipose assessment
Total body fat content (kg) was assessed using bio-electrical impedance (Bodystat1500) in all patients. Dual X-ray absorptiometry (DXA, GE Lunar system, London, UK) assessment of total fat was also performed in 26 of the 80 patients across a wide range of fat mass (8.7–74.5 kg) for validation of the bio-electrical impedance measurement. This showed excellent correlation between the two measurements ($r^2 = 0.98$, $P < 0.0001$). To assess visceral fat mass, a water-suppressed turbo spin echo transverse 5 mm slice was performed at the fourth/fifth lumbar intervertebral disc and analysed by manual contouring of visceral fat volume.[5]

Data acquisition and analysis
Left ventricular imaging. Images to measure ventricular volumes and function were obtained using a steady state-free precession sequence with an echo time (TE) of 1.5 ms and a repetition time (TR) of 3.0 ms, as previously described, on a 1.5 T MR system (Siemens, Munich, Germany).[5] Imaging was performed supine, prospectively gated and during end-expiratory breath-hold. All analysis was performed using cmr42 software (Circle Cardiovascular Imaging Inc, Calgary, Canada).[16,19] Global peak circumferential diastolic strain rates were determined by feature tracking analysis. Endocardial and epicardial LV contours were drawn on LV short axis and long axis images using a semi-automated process.

Proton magnetic resonance spectroscopy (^{1}H MRS). All 1H-MR spectroscopy, to determine both cardiac and hepatic lipid content, was performed on a 3.0 T MR system (Siemens) using a spectroscopic stimulated echo (STEAM) sequence, and water suppression using a T1- and B1-insensitive water suppression method for *in vivo* localised ^{1}H NMR spectroscopy as previously described.[20,21] A cardiac voxel was selected in the mid septum as shown in Figure 1. The optimal water suppression pulse to determine the lipid signal at 1.3 ppm was calibrated with a pulse sequence. Five measurements were acquired per breath-hold. A 2 s TR allowed for relaxation of the lipid signal in between sequential pulses, which resulted in participants holding their breath for 12–14 s. Six breath-holds were taken—five with water suppression in order to acquire lipid spectra, and one with no water suppression to define the water signal.[20,22] Data were analysed using in-house tools (Matlab, AMARES algorithm in JMRUI). Lipid content is described as a percentage (signal amplitude of lipid/signal amplitude of water × 100).

[31]Phosphorus magnetic resonance spectroscopy. All ^{31}P-MRS was performed at 3 T (Siemens Tim Trio MR system, Germany) and were acquired fasted. Volunteers were positioned prone over a modified heart/liver Siemens coil.[23] A 3D acquisition-weighted chemical shift imaging (CSI, TE = 0.3 ms) sequence was used, together with an RF pulse centred between T and u resonances to reduce noise, minimise any artefact and deliver even excitation of spectra, as previously described.[24] Voxel size was 16 × 8 × 8 mm, with field of view 240 × 240 × 200 mm. Nuclear Overhauser Enhancement was used to optimise the signal-to-noise ratio. Proton imaging was used to localise short-axis left ventricular slices. Saturation bands were placed over the skeletal muscle in the anterior chest wall, and the liver, in order to minimise potential signal contamination. The CSI grid was positioned to obtain one voxel containing mid-ventricular septal myocardium.[24] Analysis was blinded to descriptive data, and voxels selected separately. Selected spectra were fitted using the automated processing algorithm AMARES within the jMRUI software package. The accuracy of the spectral fit was interrogated using the coefficient of variation in the PCr/ATP values based on the Cramer–Rao lower bounds. Spectra were assessed as being of satisfactory quality with a coefficient of variation under 20%.[24]

Statistical analysis. Statistics were analysed using SPSS 20 (SPSS Inc, Chicago, USA). Data were assessed with the Kolmogorov–Smirnov test in order to confirm normal distribution and are demonstrated as mean ± standard deviation. Correlation, where relevant, was assessed with Pearson's correlation analysis. To determine the contributors to diastolic strain rate, stepwise multiple linear regression models were used. These multivariate models included peak diastolic strain rate as the dependent variable, and those independent variables which were found to have a significant association with it in the linear regression analysis (PCr/ATP, myocardial triglyceride content (MTGC), LV mass:volume ratio, visceral fat). Collinearity was investigated with variance inflation factor (all variables < 1.69). Residuals were normally distributed. To investigate in more detail the effect of myocardial energetic and myocardial triglyceride content on diastolic strain rate, mediator multiple regression was performed as per Preacher and Hayes,[25] with 10 000 sample bootstrapping of indirect effects (dependent variable peak diastolic strain rate, independent variable visceral fat, moderator variables MCTG, PCr/ATP, LVMVR). A probability value of $P < 0.05$ was considered significant.

RESULTS

Anthropometric data

For this analysis, the cohort was divided into quartiles of visceral fat. Owing to the stringent inclusion criteria, all quartiles were well-matched for age, blood pressure and serum cholesterol (Table 1). Although fasting glucose levels were well within the normal range for all quartiles, fasting insulin and HOMA levels were higher in the highest visceral fat quartile in line with a degree of insulin resistance with increases in visceral fat (Table 1).

Left ventricular structure

As expected, increasing BMI, total fat mass and visceral fat were associated with increasing LV mass (BMI, $r = 0.30$, $P = 0.008$; fat mass, $r = 0.22$, $P = 0.055$; visceral fat, $r = 0.39$; $P < 0.001$) and with concentric LV remodeling (BMI, $r = 0.25$, $P = 0.03$; total fat mass, $r = 0.22$, $P = 0.053$; visceral fat $r = 0.39$, $P < 0.001$).

Left ventricular diastolic function

Diastolic function was impaired in obesity, with BMI ($r = -0.37$, $P < 0.001$), total body fat ($r = -0.43$, $P = 0.001$) and visceral fat ($r = -0.46$, $P = 0.001$) all being negatively correlated with diastolic strain rate. As expected, both increasing LV concentric remodelling ($r = -0.28$, $P = 0.01$) and insulin resistance (HOMA, $r = -0.26$, $P = 0.034$) were also correlated with diastolic function. In addition, myocardial PCr/ATP ratio ($r = 0.38$, $P = 0.001$) and MTGC ($r = -0.42$, $P < 0.001$) were related to diastolic dysfunction (Table 2, Figure 2). Stepwise multivariable regression of these variables showed that both MTGC ($\beta = -0.2$, $P = 0.042$) and PCr/ATP ($\beta = -0.23$, $P = 0.046$) were independent predictors of diastolic function (overall R^2 of the model 0.29, $P = 0.001$, Table 3).

To further explore the relationship between obesity, diastolic function, MTGC and PCr/ATP, moderated multiple regression was performed (dependent variable peak diastolic filling rate, independent variable visceral fat, moderators PCr/ATP, MTGC and LVMVR, Table 4). In this visceral fat was positively related to PDSR (c pathway; $\beta = -0.003$, $P = < 0.001$), related negatively to PCr/ATP (a_1 pathway; $\beta = -0.003$, $P = < 0.01$), and positively to both MTGC (a_2 pathway; $\beta = 0.004$, $P = < 0.01$) and LVMVR (a_3 pathway; $\beta = 0.0007$, $P = < 0.01$). In addition, the mediators PCr/ATP (b_1 pathway $\beta = 0.26$, $P = 0.032$), MTGC (b_2 pathway; $\beta = -0.21$, $P = 0.016$) and LVMR (b_3 pathway $\beta = -0.57$, $P = 0.047$) were all related to PDSR. As both a and b pathways were found to be significant, mediation analysis was performed using 10 000 bootstrap resamples to calculate a bias-corrected 95% confidence interval of the indirect effect (Figure 3). This confirmed the mediating roles of PCr/ATP ($\beta = -0.008$, CI $= -0.0015$ to -0.003), MTGC ($\beta = -0.008$, CI $= -0.002$ to -0.0002) and LVMVR ($\beta = -0.004$, CI $= -0.001$ to -0.0002) in the relationship between visceral fat and PDSR. As the direct effect of body fat became non-significant ($\beta = -0.006$, $P = 0.427$), this suggests full mediation with all the effects of fat mass on diastolic function being mediated via PCr/ATP, MTGC and LVMVR in this model. When considering the negative effect of visceral fat on diastolic function, 40% was explained by increased MTGC, 39% by reduced PCr/ATP and 21% by concentric remodelling.

Myocardial energetics

Increasing obesity, whether measured by BMI ($r = -0.48$, $P < 0.001$), fat mass ($r = -0.48$, $P < 0.001$) or visceral fat ($r = -0.50$, $P < 0.001$), was associated with a decreasing PCr/ATP ratio. Within this cohort, myocardial energetics were also related to fasting glucose concentration ($r = -0.37$, $P = 0.001$) and there was a trend towards relation with fasting triglyceride levels ($r = -0.23$, $P = 0.053$).

Myocardial triglyceride content (steatosis)

Increasing obesity, whether measured by BMI ($r = 0.42$, $P < 0.001$), fat mass ($r = 0.47$, $P < 0.001$) or visceral fat ($r = 0.46$, $P < 0.001$), was associated with increasing MTGC. However, unlike myocardial energetics which showed a progressive and equally spread decrease across the increasing visceral fat quartiles, the largest increase in MTGC occurred between quartiles III and IV, where a 79% increase occurred (from 0.48 ± 36 to $0.86 \pm 0.67\%$, $P = 0.048$, Figure 2). In addition, while across quartiles I-to-III there was no significant increase in MTGC with increased visceral fat ($P = 0.238$), between quartiles III and IV there was a significant MTGC increase per cm^2 visceral fat increase (↑MTGC 0.002% per cm^2 increase in visceral fat, $P = 0.0124$). MTGC was also correlated with left ventricular hypertrophy (LV mass; $r = 0.28$, $P = 0.0121$) and with concentric LV remodelling (LVMVR $r = 0.24$, $P = 0.033$). Increasing fasting glucose ($r = 0.25$, $P = 0.032$), insulin levels ($r = 0.33$, $P = 0.004$) and insulin resistance (HOMA, $r = 0.34$, $P = 0.003$) were all correlated with increasing MTGC. Importantly, MTGC and PCr/ATP were not correlated in this study ($r = -0.17$, $P = 0.138$).

DISCUSSION

The face of heart failure has changed over recent years, with now half of new diagnoses involving preserved, as opposed to reduced, ejection fraction. Despite this, clinical trials in HFpEF have been disappointing, and current treatments are directed to targeting the co-morbidities and symptoms, rather than the intrinsic changes in diastolic function that characterise the condition. With its prevalence rapidly increasing on a global scale,

Table 1. Anthropometric data for the study group separated into quartiles

	Visceral fat quartile			
	I *n = 20*	*II* *n = 20*	*III* *n = 20*	*IV* *n = 20*
Age (years)	34.3 ± 11.0	43.0 ± 13.0	43.3 ± 15.0	45 ± 12.0
BMI (kg m^{-2})	$22.8 \pm 3.2^{\S}$	$24.7 \pm 3.3^{\S}$	$26.8 \pm 4.4^{\S}$	$36.6 \pm 7.4^{*\dagger\ddagger}$
Visceral fat (cm^2)	28 ± 9	$59 \pm 7^{*\ddagger\S}$	$94 \pm 16^{*\dagger\S}$	$182 \pm 45^{*\dagger\ddagger}$
Total fat mass (kg)	16 ± 7	$20 \pm 6\S$	$21 \pm 8^{*\S}$	$42 \pm 17^{*\dagger\ddagger}$
Systolic blood pressure (mm Hg)	118 ± 9	123 ± 12	134 ± 14	129 ± 18
Diastolic blood pressure (mm Hg)	73 ± 8	75 ± 8	79 ± 8	81 ± 8
Fasting glucose (mmol l^{-1})	$4.7 \pm 0.5^{\ddagger\S}$	$4.9 \pm 0.6^{\S}$	5.2 ± 0.6	5.4 ± 0.6
Fasting cholesterol (mmol l^{-1})	4.5 ± 0.8	4.6 ± 1.4	4.6 ± 1.1	5.0 ± 1.2
Insulin (mmol l^{-1})	8.6 ± 5.0	$9.7 \pm 6.8^{\S}$	8.9 ± 8.0	11.8 ± 6.6
HOMA-IR	1.8 ± 1.0	$2.3 \pm 1.7^{\S}$	2.1 ± 1.9	2.7 ± 1.5

Abbreviation: BMI, body mass index. *$P < 0.05$ vs Quartile I. †$P < 0.05$ vs Quartile II. ‡$P < 0.05$ vs Quartile III. §$P < 0.05$ vs Quartile IV.

Table 2. Left ventricular data for the study group separated into quartiles

	Visceral fat quartile			
	I n = 20	II n = 20	III n = 20	IV n = 20
End-diastolic volume (ml)	147 ± 33	150 ± 29	151 ± 25	164 ± 25
Stroke volume (ml)	100 ± 15	103 ± 19	107 ± 16	116 ± 19
Ejection fraction (%)	69 ± 6	69 ± 5	71 ± 4	70 ± 6
Mass (g)	104 ± 33	113 ± 32	125 ± 26	137 ± 33
Mass:volume ratio	0.70 ± 0.09	0.75 ± 0.14	0.83 ± 0.12*	0.83 ± 0.17*
Peak systolic strain (ε_{cc})	− 19.7 ± 1.7	− 19.2 ± 2.2	− 18.6 ± 1.7	− 17.7 ± 2.2*†
Peak diastolic strain rate ($s - 1/s$)	1.74 ± 0.26	1.44 ± 0.34*	1.42 ± 0.29*	1.21 ± 0.32*
PCr/ATP	2.06 ± 0.45	1.98 ± 0.31	1.69 ± 0.32*	1.57 ± 0.38*†
Triglyceride content (% water signal)	0.39 ± 0.20	0.41 ± 0.19	0.51 ± 0.43	0.84 ± 0.72*†‡§

*$P < 0.05$ vs Quartile I. †$P < 0.05$ vs Quartile II. ‡$P < 0.05$ vs Quartile III. §$P < 0.05$ vs Quartile IV.
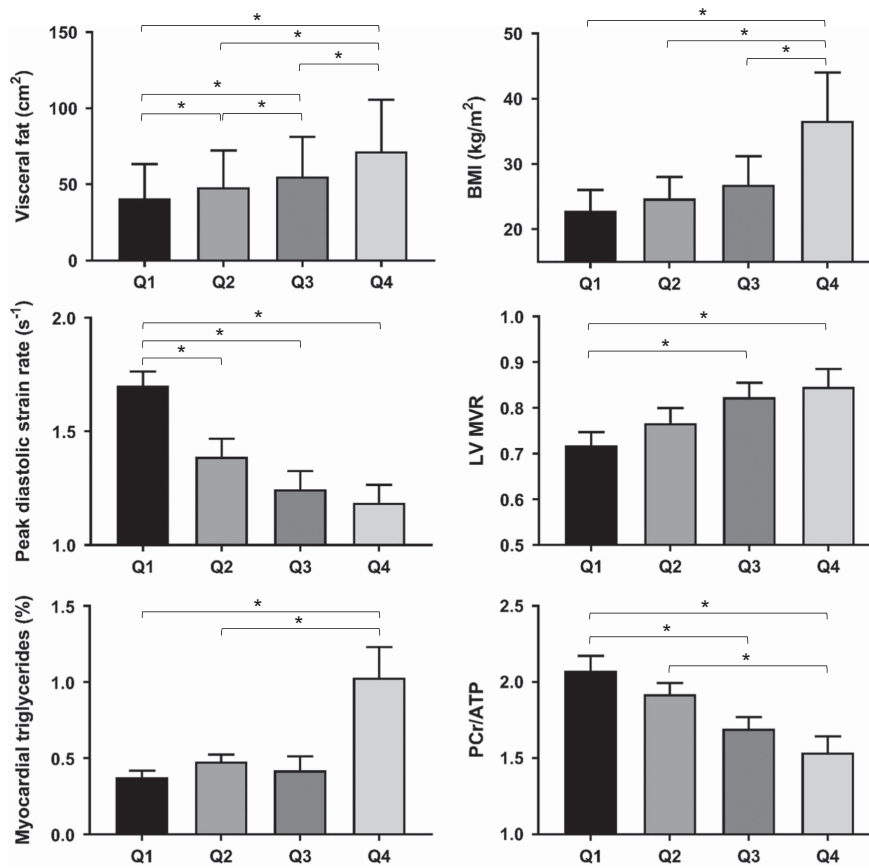
Figure 2. The effect of increasing visceral fat on diastolic strain rate, LV concentric remodelling, myocardial triglyceride content, and myocardial PCr/ATP ratio (* indicates $P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

Table 3. Regression analysis for peak diastolic strain rate

| Peak diastolic strain rate	Bivariate		Multivariate	
	r	P	β	P
MTGC (% water)	− 0.42	< 0.001	− 0.20	0.038
PCr/ATP ratio	0.38	0.001	0.23	0.038
LV mass:volume ratio	− 0.28	0.012	− 0.48	0.12
Visceral fat mass (cm²)	− 0.44	< 0.001	− 0.01	0.34

Abbreviations: LV, left ventricular; MTGC, myocardial triglyceride content.

obesity is one of the main contributors to HFpEF. However, the relative contributions of the pathophysiological mechanisms by which it causes diastolic dysfunction, including impaired myocardial energetics, lipotoxicity and concentric LV hypertrophic remodelling, remain unclear. Here we have isolated the effects of obesity on diastolic function by excluding participants with other cardiovascular risk factors, such as diabetes and hypertension, that are themselves implicated in diastolic dysfunction. As a result, we have shown that, in this model, impaired myocardial energetics, myocardial steatosis and concentric LV hypertrophic remodelling are independent predictors of diastolic impairment. This is the first study to suggest that metabolic processes, such as energetics and lipotoxicity, may have a greater contribution to

Table 4. Moderated regression analysis for peak diastolic strain rate

	Coefficient	s.e.	t	p
Visceral fat to PCr/ATP effect (a^1 pathway)	− 0.0029	0.0007	− 4.12	0.0001
Visceral fat to MTGC effect (a^2 pathway)	0.0037	0.0008	4.53	< 0.0001
Visceral fat to LVMVR effect (a^3 pathway)	0.0007	0.0002	2.88	0.005
Direct effect of PCr/ATP on PDSR (b^1 pathway)	0.26	0.1	2.64	0.01
Direct effect of MTGC on PDSR (b^2 pathway)	− 0.21	0.09	− 2.44	0.017
Direct effect of LVMVR on PDSR (b^3 pathway)	− 0.57	0.28	− 2.02	0.047
Total effect of visceral fat on PDSR (c pathway)	− 0.003	0.0006	− 4.02	0.0001
Direct effect of visceral fat on PDSR (c^1 pathway)	− 0.006	0.0008	− 0.79	0.42
Model summary		$R^2 = 0.35$, F = 8.9, $P < 0.0001$		

Abbreviation: MTGC, myocardial triglyceride content.
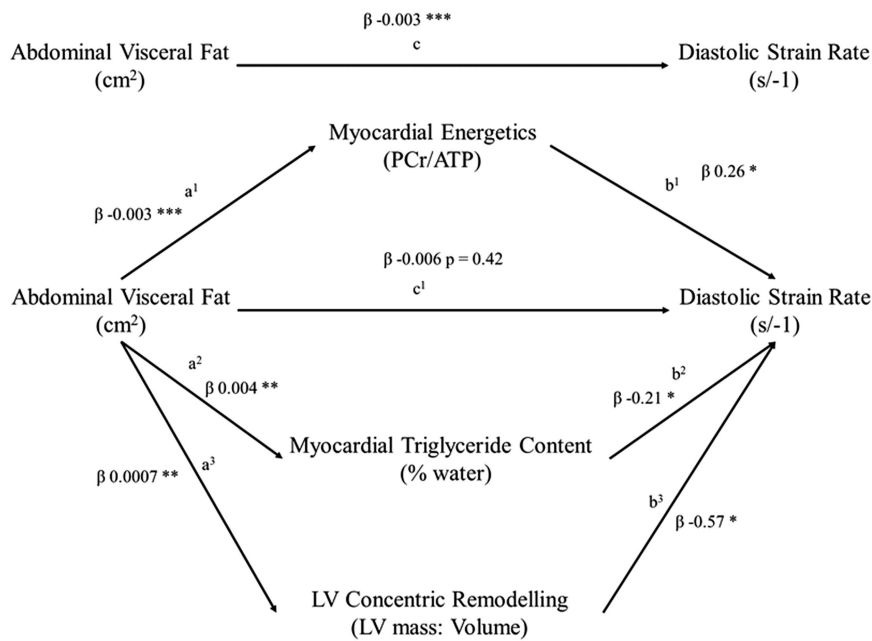
Figure 3. Moderated regression modelling of the effect of increasing visceral fat on diastolic strain rate, with moderators of LV concentric remodelling, myocardial triglyceride content and myocardial PCr/ATP (* indicates $P < 0.05$, **$P < 0.01$, ***$P < 0.001$).

impaired myocardial relaxation than changes in LV geometry and concentric LV remodelling.

The impact of myocardial energetics on diastolic function in obesity

In this study we confirm that visceral obesity is not only related to impaired myocardial energetics (by 24% in the highest visceral fat quartile), but also that this fall in energetics is associated with diastolic dysfunction. Overall, 39% of the negative effect of visceral fat on diastolic dysfunction is mediated through reduced myocardial energetics.

The most likely mechanism for the reduced PCr/ATP seen at rest here with increasing visceral obesity is a diminished total creatine store, which is proportional to the reduction in PCr, and typically seen in cardiac hypertrophy.[26] If [ATP] remains constant, it follows from the creatine kinase equilibrium expression that PCr depletion implies increased steady-state [ADP] and reduced energy generated by hydrolysis of ATP's gamma-phosphoryl moiety. Increased metabolism of free fatty acids in obesity alters the mitochondrial redox state and reduces mitochondrial efficiency—as a result the overall ATP yield normalised to oxygen consumption is likely to be lower.[18,27–29] Indeed, it has been shown that if the isolated pig heart is perfused with fatty acids, the same workload requires

additional oxygen by more than 25% in comparison with glucose.[30] This inefficiency has also been shown in obese humans using PET.[31] The diastolic phase of the cardiac cycle is more sensitive to energetic depletion, due to the higher energy demands of active calcium uptake via SERCA, relative to myosin ATPase. It is therefore logical that compromises in myocardial energetics are linked to diastolic dysfunction.

Adipose tissue expansion and myocardial lipotoxicity

The most physiological depot in which to store excess lipids is the white subcutaneous adipose tissue. However, once its capacity is replete, excess fat can 'overspill' into less physiologically appropriate, non-adipose tissues.[32] The deposition of fat into non-adipose depots occurs in both the apparently opposite pathological states of lipodystrophy[33] and obesity,[17] where storage capacity is exceeded either due to a congenital absence of white adipose tissue, or via an excess supply of lipid, respectively. When the excess fat is directed to the heart, the initial response is to store the surplus in the form of triacylglycerol. However, the buffering capability in the heart is limited, and thereafter lipids enter alternative pathways, resulting in creation of toxic reactive lipid species (such as ceramides and diacyl-glycerol).[34]

We have shown here that a nearly twofold greater increase in MTGC occurs between visceral fat quartiles III and IV when compared to the increment between quartiles I and III. This is in line with the hypothesis that there is an initial protective buffering effect of visceral fat, which, when saturated, results in much greater cardiac TG deposition.

Concentric left ventricular hypertrophy and diastolic function

Cardiac output and circulating volume are both increased in obesity, which over time leads to cardiovascular volume overload. Contrary to earlier studies which described an association with concentric LV remodelling,[35,36] it is now clear that obesity leads to a more eccentric pattern of remodelling, with increases in both cavity size and wall thickness. This increase in wall thickness changes the intrinsic mechanical properties of the myocardium, acting as one of the main passive mechanisms of diastolic impairment. Here we have shown that concentric LV remodelling indeed independently predicts diastolic function—however, it only accounts for around 20% of the effect of visceral fat on diastolic function, around half of the effect of MTGC and energetics.

The severity of concentric LV remodelling seen in obesity[5,37] may reflect altered adipokine environment with hyperleptinaemia and hyperinsulinaemia both being linked to increased cardiomyocyte size and left ventricular hypertrophy in human obesity.[38,39] The myocardium itself expresses isoforms of the leptin receptor,[40] and even in isolation, activation of these induces hypertrophy in cardiomyocyte culture.[41–44] While leptin leads to hypertrophy via pathways involving JAK/STAT, MAPK, protein kinase C and Rho/ROCK dependent kinases,[45–47] hyperinsulinaemia also has a role, acting via the plentiful myocardial insulin-like growth factor 1 receptors.[48] In addition, as described above, the presence of myocardial steatosis is also linked to concentric LV hypertrophy and remodelling, thus linking altered myocardial substrate utilisation, via overuse of fatty acid, again to diastolic dysfunction via concentric LV remodelling.

Potential treatments for diastolic dysfunction in obesity

This study reaffirms the importance of myocardial metabolism for diastolic function in obesity, perhaps contributing more than the intrinsic changes in myocardial stiffness brought about by LV concentric hypertrophy. As lipid metabolism seems to underpin both the metabolic and hypertrophic mechanisms seen here, this may be a common pathway to target as therapy, and animal models have shown that targeting the lipid metabolism pathway has the potential to be beneficial. Treatment of MHC-ACS mouse with a hepatic adenovirus encoding leptin improved contractility, presumably via increased myocardial fatty acid oxidation rates and reducing lipotoxicity.[49] In addition, treatment of the obese Zucker Diabetic Fatty rats with troglitazone reduces cardiac triglyceride, and prevents both apoptosis and loss of function.[50] Whether one specific therapeutic target can address diastolic dysfunction in human obesity remains unclear, but as reduced myocardial energetics, myocardial steatosis and concentric remodelling have all been related to overuse of lipids, this is a potential metabolic hub to address diastolic dysfunction. Ideally this would be achieved through successful weight loss interventions, which improve energetics,[51] steatosis[52] and LV remodelling,[10] but the poor sustainability of non-surgical weight loss interventions makes a pharmacological approach potentially a more realistic prospect.

CONCLUSION

Although obesity is a prime contributor to diastolic dysfunction, the mechanisms that underlie this are not well understood. Here we have shown that visceral obesity is not only related to diastolic dysfunction, but also that all of the negative effects of visceral fat on diastolic function can be accounted for by concentric LV remodelling, elevated myocardial triglyceride levels and impaired energetics. We have also shown for the first time that metabolic mechanisms may be more important than structural factors in mediating the negative effects of obesity on diastolic function. A therapeutic approach that alters myocardial substrate selection may target both the cardiac metabolic and structural effects of obesity, and is likely to be effective in treating cardiac dysfunction in obesity.

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