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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Obesity modifies the energetic phenotype of dilated cardiomyopathy

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Aims We sought to determine if myocardial energetics could distinguish obesity cardiomyopathy as a distinct entity from dilated cardiomyopathy.

Methods and results Sixteen normal weight participants with dilated cardiomyopathy (DCM_{NW}), and 27 with DCM and obesity (DCM_{OB}), were compared to 26 normal weight controls (CTL_{NW}). All underwent cardiac magnetic resonance imaging and ^{31}P spectroscopy to assess function and energetics. Nineteen DCM_{OB} underwent repeat assessment after a dietary weight loss intervention. Adenosine triphosphate (ATP) delivery through creatine kinase (CK flux) was 55% lower in DCM_{NW} than in CTL_{NW} ($P = 0.004$), correlating with left ventricular ejection fraction (LVEF, $r = 0.4$, $P = 0.015$). In contrast, despite similar LVEF (DCM_{OB} 41 ± 7%, DCM_{NW} 38 ± 6%, $P = 0.14$), CK flux was two-fold higher in DCM_{OB} ($P < 0.001$), due to higher rate through CK [median k_f 0.21 (0.14) vs. 0.11 (0.12) s^{-1}, $P = 0.002$]. During increased workload, the CTL_{NW} heart increased CK flux by 97% ($P < 0.001$). In contrast, CK flux was unchanged in DCM_{NW} and fell in DCM_{OB} (by >50%, $P < 0.001$). Intentional weight loss was associated with positive left ventricular remodelling, with reduced left ventricular end-diastolic volume (by 8%, $P < 0.001$) and a change in LVEF (40 ± 9% vs. 45 ± 10%, $P = 0.002$). This occurred alongside a fall in ATP delivery rate with weight loss (by 7%, $P = 0.049$).

Conclusions In normal weight, DCM is associated with reduced resting ATP delivery. In obese DCM, ATP demand through CK is greater, suggesting reduced efficiency of energy utilization. Dietary weight loss is associated with significant improvement in myocardial contractility, and a fall in ATP delivery, suggesting improved metabolic efficiency. This highlights distinct energetic pathways in obesity cardiomyopathy, which are both different from dilated cardiomyopathy, and may be reversible with weight loss.

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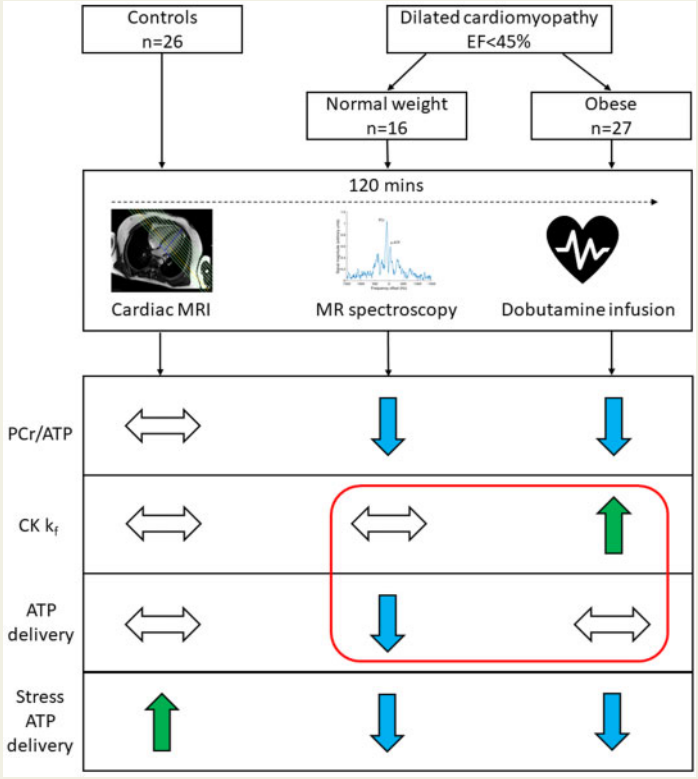
Graphical Abstract



Myocardial energetics are different in obese individuals with cardiomyopathy compared to normal weight with maintained resting adenosine triphosphate delivery. Weight loss reverses this difference and improves left ventricular systolic function. CK, creatine kinase; EF, ejection fraction; k_f, pseudo-first order forward rate constant; PCr/ATP, phosphocreatine to adenosine triphosphate ratio.

Keywords Heart failure • Obesity • Cardiac magnetic resonance imaging • Magnetic resonance spectroscopy • Cardiac energetics • Weight loss

Introduction

In the healthy heart, cardiac output varies to match the body's circulatory demands. When cardiac output increases, adenosine triphosphate (ATP) demand increases, and this must be matched with ATP supply to allow normal contractile performance. This concept underpins the suggested role of energy metabolism in heart failure—that a mismatch between ATP delivery and supply may be the common pathway underlying systolic dysfunction. Insufficient energy supply, as measured by reduced myocardial phosphocreatine/ATP ratio (PCr/ATP)[1] and reduced ATP delivery through creatine kinase (CK), has not only been shown in the transition to heart failure in pressure overload[2] but has also been linked to mortality in dilated cardiomyopathy.[3]

However, cardiac dysfunction could also occur if the demand for ATP outstripped supply, or if the efficient conversion of ATP into contractile force were impaired. While in obesity in the absence of heart failure, PCr/ATP is low,[4] we have recently shown that the forward rate constant of the CK reaction was increased,[5] in response to greater resting energy demand with normal systolic function. If ATP delivery was still preserved in the context of both obesity and systolic dysfunction, where energy demand is lower, it may reflect the inefficiency of energy utilization; this has yet to be established.

If this were the case, obesity cardiomyopathy could not only be distinct in terms of energy delivery from dilated cardiomyopathy (where ATP delivery is low) but also would be amenable to therapies that improve cardiac efficiency. As weight loss has been shown to reduce left ventricular (LV) hypertrophy,[6] haemodynamic load, improved insulin sensitivity,[7] and cardiac lipid content,[8] this should result in improved cardiac function.

We sought to investigate whether the energetic differences observed in obesity remained valid in systolic dysfunction, to assess whether specific, targeted therapeutic approaches were necessary in this cohort, as well as understand the impact of intentional weight loss on myocardial metabolism. We used a protocol combining cardiovascular magnetic resonance imaging (MRI) and cardiac ^{31}P magnetic resonance spectroscopy (MRS) to record cardiac function and

energetics in participants with established dilated cardiomyopathy, who were obese or of normal weight. This was compared to normal weight participants with normal cardiac function. Capacity to augment CK flux in response to dobutamine stress was also assessed. To investigate the effects of weight loss, studies were repeated after a dietary weight loss intervention.

Methods

In brief, the study was approved by the local ethics board (NRES reference 14/SC/004) in accordance with the Declaration of Helsinki. Patients with established idiopathic dilated cardiomyopathy (ejection fraction 25–45%) were recruited from heart failure clinics at a tertiary referral cardiology centre. Normal weight controls with normal systolic function were recruited by poster advertisement. All participants signed written consent for the study investigations.

Inclusion criteria

Participants were excluded if they had any history of coronary artery disease, severe valvular disease, were in New York Heart Association Class IV, or had any significant family history of heart failure. In addition, uncontrolled hypertension (resting blood pressure >180/90 mmHg) or atrial fibrillation (heart rate >110 b.p.m.), and previously diagnosed diabetes mellitus were exclusion criteria, as was any contraindication to magnetic resonance scanning.

Anthropomorphic and biochemical assessment

Height, weight, and body composition were measured using digital scales with bio-impedance analysis (InBody 770, InBody Co Ltd, South Korea). Body surface area (BSA) was calculated using the Mosteller formula [BSA (m^2) = $\sqrt{}$((height × weight)/3600)]. Non-invasive blood pressure was measured according to standardized methods (average of three supine measurements with an automatic sphygmomanometer, Carescape V100, GE). Fasting venous blood was drawn and biomarkers were analysed either by the Oxford University Hospitals clinical biochemistry laboratory according to standardized protocols, or by commercially available ELISA kit (leptin; Sigma-Aldrich, St Louis, MO, USA). Fasting insulin resistance was represented by HOMA-IR [(glucose × insulin)/22.5].

Magnetic resonance imaging

Magnetic resonance imaging and spectroscopy were acquired on a 3-T MR system (Tim Trio, Siemens Healthineers, Germany). Cardiac images to quantify ventricular volumes and function were acquired using an SSFP sequence (echo time 1.5 ms, repetition time 3 ms), which was performed with cardiac triggering and during end-expiratory breath-hold. Endocardial and epicardial LV contours were drawn manually and analysed using a semi-automated system (cmr42, Circle Cardiovascular Imaging Inc., Calgary, Canada). Left ventricular stroke work was calculated as stroke volume × mean arterial pressure (diastolic blood pressure + 1/3 pulse pressure). Rate pressure product was calculated as heart rate x systolic blood pressure. Cardiac MRI data were analysed by two experienced observers (J.J.R./O.J.R.), blinded to group, and timepoint in the obese cohort.

^{31}Phosphorus magnetic resonance spectroscopy

^{31}P-MRS was performed on the same 3-T system described above, with a 10-cm loop transmit-receive ^{31}P surface coil (Pulse Teq, Chobham, UK). The CK forward rate constant k_f was measured using a modified 1D-CSI Triple Repetition Saturation Transfer[9] sequence with a shorter 'stressed saturation transfer' extension[10] as previously described.

The relative ratio of PCr to γ-ATP peaks in the fully relaxed spectrum was used to generate a PCr/ATP ratio, and the rate of ATP delivery, or CK flux was calculated by $k_f \times$ [PCr] where [PCr] is calculated by multiplying PCr/ATP by literature values for [ATP] [5.7 for normal weight controls (CTL_{NW}), 5.2 for normal weight participants with dilated cardiomyopathy (DCM_{NW}) and DCM and obesity (DCM_{OB})].[11] As measurements of CK k_f were acquired supine, an adjustment factor of 1.333 was applied in order to align values with the published normal range (acquired prone), the rationale for which has previously been described;[10] hence, all k_f values reported throughout the manuscript have been adjusted using this scaling factor. This has been validated against cardiac biopsy samples as previously published.[2] 31P-MRS data were analysed *post hoc* using in house automated software within Matlab as previously described.[10,12]

Dobutamine stress measurements

Beta-blocker therapy was withheld for a period of 48 h prior to study visit. Dobutamine was infused via a peripheral venous cannula, at incremental doses between 5 and 40 μg/kg/min as necessary to achieve the target heart rate of 65% maximum (maximum heart rate calculated as 220—age). Cine images were repeated at maximum stress to assess contractile response to stress, as well as exclude any regional wall motion abnormalities, and stress ^{31}P measurements acquired. Average time of infusion was 24 min.

Echocardiography

Echocardiography was performed on a Philips Epiq (Philips, Netherlands) system to determine diastolic function; pulse wave velocity was measured at mitral valve inflow to calculate E/A ratio, and tissue Doppler at lateral and medial mitral valve annulus to generate E/e′ ratios, as well as the mean of medial and lateral velocities.

Six-minute walk test

All participants underwent a standardized walking test[13] along a 35-m corridor for 6 min. The total distance achieved was recorded.

Weight loss intervention

The obese volunteers underwent dietary weight loss advice with telephone/email support from the study team. They adhered to a calorie-controlled (up to 1500 kcal), low glycaemic index diet for a median 336 days [interquartile range (IQR) 216–432]. Volunteers were encouraged to maintain current activity levels during this timeframe.

Statistical analysis

Statistical analysis was performed using commercial software (SPSS 24, Chicago, IL, USA). All data are presented as mean ± standard deviation or median (IQR) where stated. Normality was assessed using a Shapiro–Wilk test. Parametric (paired and independent two-sided Student's *t*-tests) and non-parametric tests (independent samples Kruskal–Wallis test; related samples Wilcoxon signed rank test) were used as appropriate. Significance across multiple groups was assess using one-way ANOVA, with Bonferroni correction. Pearson's correlation and linear regression were used. *P*-values of <0.05 were considered as statistically significant.

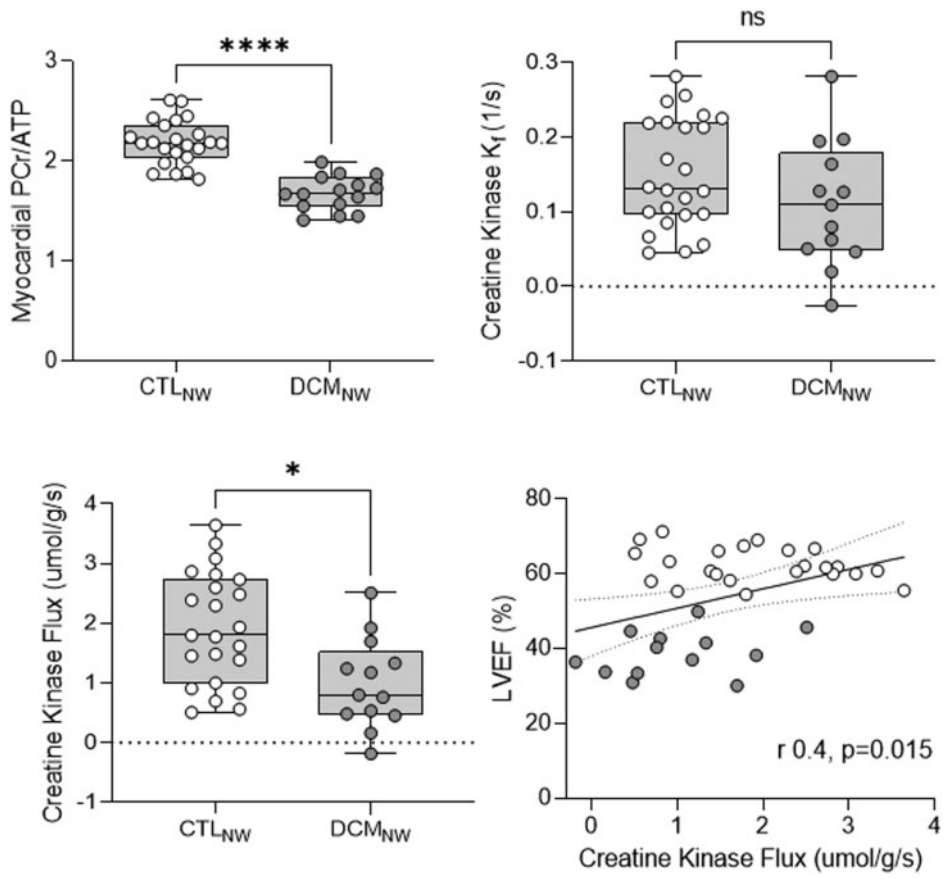


Figure 1 The relationship between cardiac energetics and left ventricular systolic function in normal weight participants (white circles indicate controls, grey circles dilated cardiomyopathy). CTL_{NW}, normal weight controls, DCM_{NW}, normal weight participants with dilated cardiomyopathy; LVEF, left ventricular ejection fraction; ns, non-significant; PCr/ATP, phosphocreatine to adenosine triphosphate ratio. *p<0.05; ****p<0.001.

Results

Myocardial energetics and dilated cardiomyopathy

Twenty-six normal weight [body mass index (BMI) 23 ± 2 kg/m^2] volunteers with normal systolic function [LV ejection fraction (LVEF) 62 ± 5%; CTL_{NW}] and 16 normal weight (BMI 23 ± 2 kg/m^2) participants with DCM (LVEF 38 ± 6%; DCM_{NW}) were studied.

Myocardial PCr/ATP was lower in DCM_{NW} (1.7 ± 0.2 vs. 2.2 ± 0.2, $P < 0.001$), as expected. Median CK k_f was similar between DCM_{NW} [0.11 (0.17) s^{-1}] and CTL_{NW} [0.13 (0.12) s^{-1}, $P = 0.12$]. As a result, median ATP delivery through CK flux was significantly lower in DCM_{NW} [0.8 (1.0) vs. CTL_{NW} 2.0 (1.6) µmol/g/s, $P = 0.004$; *Figure 1*]. In addition, in these normal weight participants, CK flux was correlated with LVEF ($r = 0.4$, $P = 0.015$; *Figure 1*).

The impact of obesity in dilated cardiomyopathy

Baseline characteristics

The DCM_{NW} cohort was compared with 27 participants with DCM (LVEF 40 ± 7%) and obesity (BMI 37 ± 5 kg/m^2; DCM_{OB}). The two groups were well-matched for age (normal weight 59 ± 16 years, obese 57 ± 11 years, $P = 0.748$), sex (63% male in both groups, $P = 0.976$), blood pressure, and fasting total cholesterol (*Table 1*). As expected, the obese group had significantly higher baseline body fat mass ($P < 0.001$) and circulating triglycerides ($P = 0.008$) and were significantly more insulin resistant, with higher fasting glucose (6.4 ± 2.2 vs. 5.2 ± 0.6 mmol/L, $P = 0.025$) and HOMA-IR (8.9 ± 7.5 vs. 3.1 ± 2.0, $P = 0.002$).

The two groups had similar cardiac morphology, with no significant differences between LV end-diastolic volume, stroke volume, and ejection fraction (normal weight 38 ± 6% vs. obese 41 ± 7%, $P = 0.147$; *Table 1*). Left ventricular stroke work was similar between the groups (normal weight 7.9 ± 2.5 L mmHg, obese 8.9 ± 2.1 L mmHg; $P = 0.242$). BNP levels were also similar between the two groups (21 ± 25 vs. 39 ± 43 mmol/L, $P = 0.07$).

Pharmacological therapy was also similar between the two DCM groups, with similar numbers taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (89% in DCM_{OB}, 94% in DCM_{NW}, $P = 0.845$) and beta-blockers (69% in DCM_{NW}, 82% in DCM_{OB}, $P = 0.224$).

Despite very similar cardiac morphology and pharmacological therapy, the obese group was more significantly limited in terms of

Table 1 Baseline characteristics of the cohorts

	CTL_{NW} ($n = 26$)	DCM_{NW} ($n = 16$)	DCM_{OB} ($n = 27$)	*P*-value
Anthropometrics				
Age (years)	47 ± 18	59 ± 16	57 ± 11	**0.001**[a]
Male sex, *n* (%)	9 (35)	10 (63)	17 (63)	0.076
Body mass index (kg/m^2)	23 ± 2	23 ± 2	37 ± 5	**<0.001**[b]
Systolic blood pressure (mmHg)	123 ± 19	125 ± 25	129 ± 16	0.302
Diastolic blood pressure (mmHg)	74 ± 13	72 ± 18	81 ± 14	0.148
Resting heart rate (b.p.m.)	57 ± 8	63 ± 10	72 ± 15	**<0.001**[a]
Metabolic status				
Total cholesterol (mmol/L)	4.6 ± 1.0	5.0 ± 1.1	4.8 ± 1.0	0.560
Triglycerides (mmol/L)	1.0 ± 0.5	1.3 ± 0.6	2.1 ± 1.2	**0.001**[b]
Fasting glucose (mmol/L)	4.8 ± 0.4	5.2 ± 0.6	6.4 ± 2.2	**0.006**[b]
Fasting insulin (mmol/L)	50 ± 25	64 ± 34	142 ± 78	**<0.001**[b]
HOMA-IR	2.0 ± 1.0	3.1 ± 2.0	8.9 ± 7.5	**<0.001**[b]
BNP (mmol/L)	7 ± 5	39 ± 43	21 ± 25	**<0.001**[a,c]
Drug therapy				
ACE inhibitor	—	13 (81)	17 (65)	0.269
Angiotensin receptor blocker	—	2 (13)	7 (26)	0.269
Beta-blocker	—	11 (69)	22 (82)	0.224
Aldosterone antagonist	—	8 (50)	11 (41)	0.627
Loop diuretic	—	6 (38)	11 (41)	0.130
Left ventricle				
End-diastolic volume (mL)	145 ± 22	210 ± 47	227 ± 58	**<0.001**[a]
End-systolic volume (mL)	55 ± 11	143 ± 61	136 ± 46	**<0.001**[a]
Stroke volume (mL)	90 ± 15	86 ± 32	91 ± 20	0.761
Ejection fraction (%)	62 ± 5	38 ± 6	41 ± 7	**<0.001**[a]
Mass (g)	98 ± 16	144 ± 41	163 ± 38	**<0.001**[a]
LV stroke work (L mmHg)	8.0 ± 1.7	7.9 ± 2.5	8.9 ± 2.1	0.242
Left atrial volume (mL)	56 ± 15	85 ± 33	97 ± 30	**<0.001**[a]
Right ventricle				
End-diastolic volume (mL)	142 ± 31	137 ± 38	153 ± 36	0.156
End-systolic volume (mL)	51 ± 17	56 ± 28	61 ± 23	0.067
Ejection fraction (%)	65 ± 7	61 ± 12	61 ± 9	0.122
Functional capacity				
Six-minute walk test distance (m)	596 ± 31	574 ± 102	500 ± 104	**0.011**[b]

ACE, angiotensin-converting enzyme; BNP, beta natriuretic peptide; CTL_{NW}, normal weight controls, DCM_{NW}, normal weight participants with dilated cardiomyopathy; DCM_{OB}, DCM and obesity; LV, left ventricular. Bold type indicates significant difference.
[a]Significant difference between control group and dilated cardiomyopathy groups.
[b]Significant difference between normal weight groups and obese group.
[c]Kruskal–Wallis test for non-parametric BNP data.

functional capacity on 6-min walk test distance (500 ± 104 m compared to 574 ± 102 m, $P = 0.008$).

Effect of obesity on myocardial energetics in dilated cardiomyopathy

Phosphocreatine/ATP was similarly reduced in DCM_{OB} and DCM_{NW} groups (1.7 ± 0.3 vs. 1.7 ± 0.2, $P = 0.480$). The median CK k_f was significantly higher in DCM_{OB} than DCM_{NW} [0.21 (0.14) vs. 0.11 (0.13) s^{-1}, $P < 0.001$; *Figure 2*] and correlated positively with body fat ($r = 0.426$ where r is Pearson's correlation coefficient, $P = 0.027$). As a result, median CK flux was higher in DCM_{OB} than in DCM_{NW} [2.0 (1.6) vs. 0.8 (1.0) μmol/g/s, $P = 0.002$; *Figure 2*] and also correlated with fat mass ($r = 0.42$, $P = 0.029$; *Figure 2*).

The effect of increased workload in dilated cardiomyopathy

Twenty CTL_{NW}, 15 DCM_{OB}, and 7 DCM_{NW} consented to undergo dobutamine infusion to increase workload. Infusion times and peak heart rate were similar (CTL_{NW}: 24 ± 3 min, 113 ± 8 b.p.m., 64 ± 4% maximum heart rate; DCM_{NW}: 24 ± 3 min, 113 ± 8 b.p.m., 64 ± 4% maximum heart rate; DCM_{OB}: 24 ± 3 min, 108 ± 8 b.p.m., 68 ± 7% maximum heart rate). Left ventricular ejection fraction augmentation

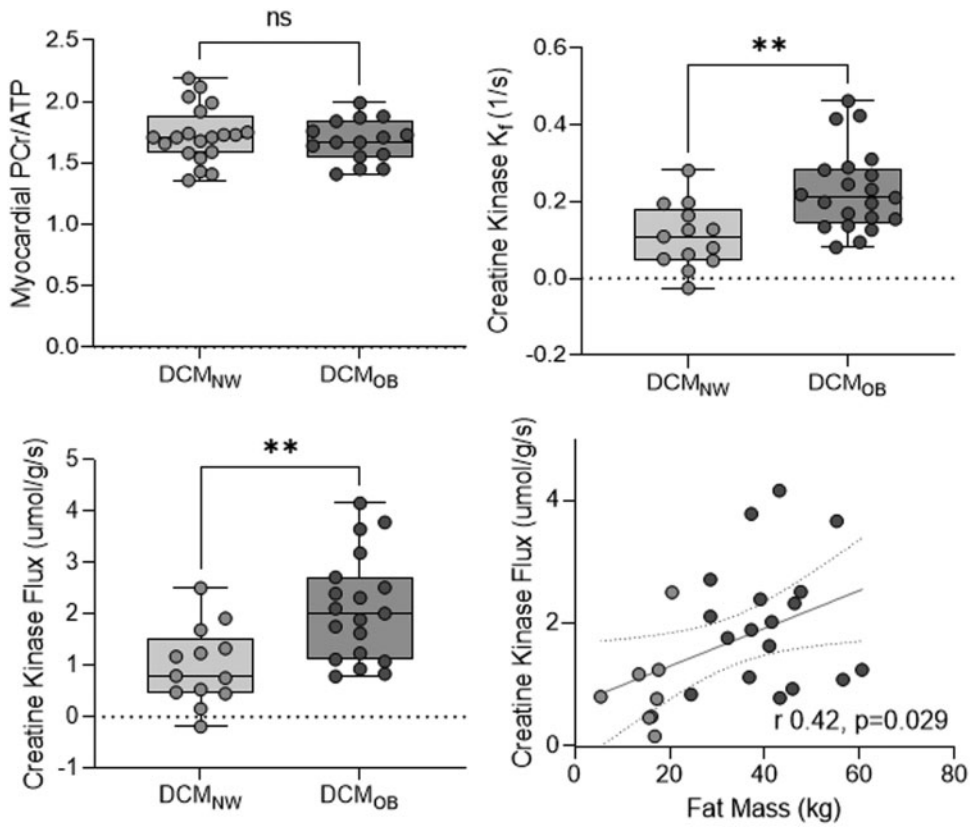


Figure 2 Comparison of myocardial energetics in obese and normal weight individuals with dilated cardiomyopathy (light grey circles indicate normal weight dilated cardiomyopathy, dark grey circles obese dilated cardiomyopathy). DCM_{NW}, normal weight participants with dilated cardiomyopathy; DCM_{OB}, DCM and obesity; ns, non-significant; PCr/ATP, phosphocreatine to adenosine triphosphate ratio. **p<0.01.

was also similar between groups (absolute increase in LVEF CTL_{NW} 17 ± 6%, DCM_{OB} 16 ± 10%, DCM_{NW} 16 ± 6%, *Figure 3*).

In CTL_{NW} hearts, increased workload was associated with no change in PCr/ATP, median CK k_f increased 1.9-fold ($P < 0.001$), and median CK flux also increased by 60% ($P < 0.001$; *Figure 3*).

In contrast, during similar workload, and with similar LVEF augmentation, in DCM_{NW}, heart's PCr/ATP fell (rest 1.7 ± 0.2 to stress 1.3 ± 0.5, $P = 0.034$), and there was no increase in either median CK k_f [rest 0.11 (0.18) to stress 0.11 (0.14) s^{-1}, $P = 0.93$] or CK flux [rest 0.8 (1.1) to stress 0.6(0.8) μmol/g/s, $P = 0.99$].

However, during similar workload, and again with similar LVEF augmentation (*Figure 3*), in DCM_{OB}, heart's PCr/ATP also fell (from 1.7 ± 0.3 to 1.0 ± 0.2, $P < 0.001$), with a trend to a reduction in median CK k_f [rest 0.22 (0.12) to stress 0.19 (0.18) s^{-1}, $P = 0.11$] and a fall in CK flux [rest 2.0 (1.5) to stress 1.0 (1.2) μmol/g/s, $P = 0.016$].

The effect of intentional weight loss in obese dilated cardiomyopathy

During the study period of 11 months [336 days (IQR 216–432)], 8 (30%) DCM_{OB} withdrew from the study (6 device implantation, 2 withdrawal of consent). Of the 19 who completed the intervention, 12 were successful in losing weight, with a mean loss 6 ± 4% body weight. All individuals were included in the analysis, in an intention-to-treat model, unless otherwise specified (for results broken down by success of weight loss intervention, see Supplementary material online, *Table S1*). There were no significant changes in pharmacotherapy in terms of drugs prescribed or doses after the weight loss intervention.

Cardiovascular effects of successful weight loss

Following the weight loss intervention, there was positive cardiac remodelling in the DCM_{OB} group, with a significant reduction in LV cavity size (*Graphical abstract*). In addition, weight loss was associated with a significant improvement in LV systolic function (LVEF +7 ± 5%, $P = 0.002$), driven by a greater fall in end-systolic volume (151 ± 64 vs. 128 ± 69 mL, $P = 0.008$). There was no significant change in LV stroke volume (93 ± 17 vs. 96 ± 22 mL, $P = 0.467$), or mean arterial pressure (94 ± 12 vs. 93 ± 9 mmHg, $P = 0.977$), and calculated LV stroke work did not change significantly ($P = 0.499$). Functional capacity improved without reaching statistical significance (6-min walk test distance 505 ± 76 to 532 ± 59 m, $P = 0.057$).

Myocardial energetics and weight loss

In DCM_{OB}, the weight loss intervention resulted in no change in PCr/ATP (pre 1.7 ± 0.3, post 1.8 ± 0.5, $P = 0.90$), a numerical fall in median CK k_f [pre 0.21 (0.15), post 0.18 (0.15) s^{-1}, $P = 0.23$], and a 6% fall in median CK flux [pre 1.6 (1.4), post 1.5 (1.3) μmol/g/s, $P = 0.048$; *Figure 4*].

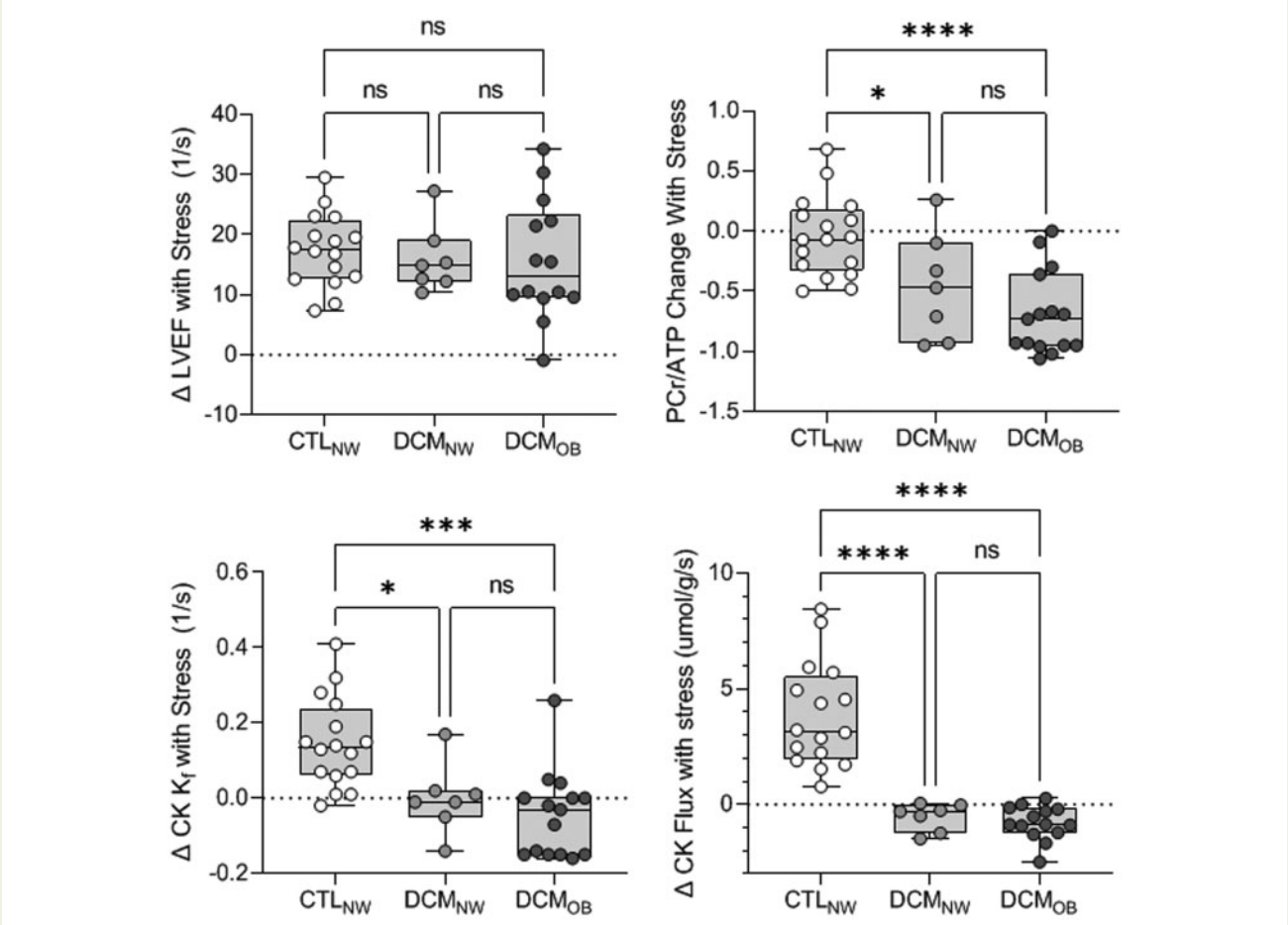


Figure 3 Cardiac energetics and function during increased workload; a comparison of normal hearts and dilated cardiomyopathy in obese and normal weight volunteers. CK, creatine kinase; CTL_{NW}, normal weight controls, DCM_{NW}, normal weight participants with dilated cardiomyopathy; DCM_{OB}, DCM and obesity; LVEF, left ventricular ejection fraction; ns, non-significant; PCr/ATP, phosphocreatine to adenosine triphosphate ratio. *p<0.05; ***p<0.005; ****p<0.001.

Weight loss and energetics during increased workload

Seven of the DCM_{OB} group consented to repeat dobutamine stress testing. This showed that following the weight loss intervention, there were no fall in PCr/ATP during dobutamine stress (rest 1.5 ± 0.4, stress 1.6 ± 0.2, $P = 0.37$), an increase in median CK k_f [rest 0.18 (0.14), stress 0.22 (0.10) s^{-1}; $P = 0.016$], and an increase in CK flux [rest 1.7 (2.5), stress 2.0 (2.3) μmol/g/s, $P = 0.016$] when comparing post-intervention results to the same individuals' results at baseline (*Figure 5*).

As a result, the energetic response to increased workload following successful weight loss in a small group of individuals is closer to that seen in obese individuals with normal systolic function[5] and suggests that the resting values are now not reflective of the maximum CK capacity.

Discussion

In this study looking at ATP delivery in heart failure, we have shown that, while myocardial ATP delivery rate through CK is reduced in patients with DCM and normal weight and is related to reduced systolic function, CK flux is higher in obese DCM patients with a similar degree of LV dysfunction. This is such that CK flux in obese DCM is similar to normal weight participants with normal systolic function. This suggests that the DCM heart in obesity is less energy efficient. In addition, we have shown that, while ATP delivery rate increases in the normal heart during increased workload, the heart in normal weight DCM is unable to do so, and that ATP delivery even falls in obese DCM hearts. Furthermore, we show that weight loss is accompanied by LV systolic recovery alongside reduced ATP delivery rate, suggesting that weight loss improves myocardial energetic efficiency.

Myocardial energetics in normal weight heart failure

A final common pathway in heart failure culminating in systolic dysfunction may occur when the energy demand of the myocardium outstrips supply. In line with this and other previous studies in heart failure,[3] we have shown that ATP delivery through CK is reduced in DCM, and is correlated to LVEF. This would suggest that reduced ATP delivery is playing a role in the cardiac dysfunction in DCM.

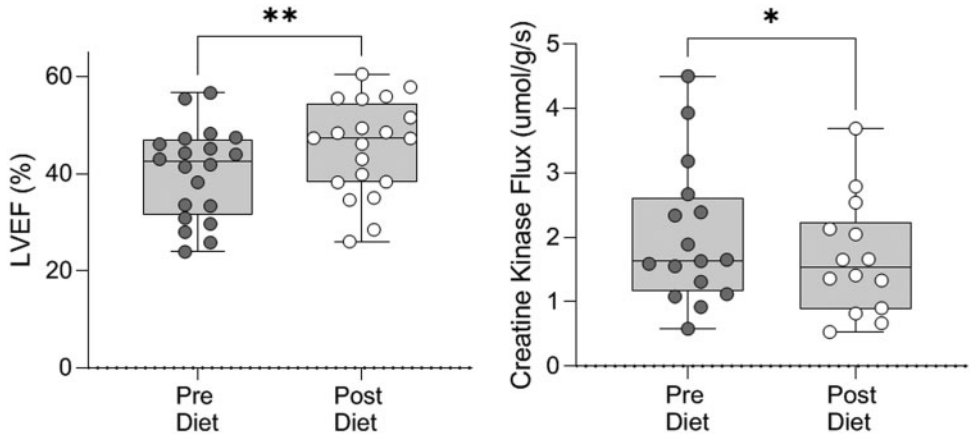


Figure 4 The effect of weight loss on left ventricular systolic function and myocardial adenosine triphosphate delivery rate. LVEF, left ventricular ejection fraction. *p<0.05; **p<0.01.

However, in contrast to this, despite similar LVEF and stroke work, ATP delivery through CK in DCM_{OB} was elevated, and similar to normal hearts at rest. This would suggest that the DCM_{OB} heart is less energy efficient, demanding more ATP to deliver the same stroke work. It could be inferred that it is myocardial inefficiency driving systolic dysfunction in DCM_{OB}, with resting ATP demand already exceeding maximal ATP delivery.

This would be in keeping with the known pathophysiology of the insulin-resistant[14] obese heart. Across animal[15] and human studies,[16] obesity consistently causes increased fatty acid availability, uptake and utilization, resulting in reduced myocardial efficiency (cardiac work per myocardial oxygen consumption). In addition, over time, a mismatch between uptake and oxidation leads to the accumulation of fatty acid intermediates,[17] increased reactive oxygen species generation, and oxidative stress, which cause cardiomyocyte apoptosis and impairment of cardiac function.

On the other hand, in severe obesity, increased expression of mitochondrial uncoupling proteins[18] reduces efficiency within the electron transport chain and eventually a fall in production of ATP itself. It seems that in this cohort with moderate LV impairment, resting ATP production is maintained, perhaps preceding a transition to impaired ATP generation in more severe disease.

When put together with this study showing resting ATP delivery rate is higher in DCM_{OB} than in DCM_{NW}, it is likely that obesity cardiomyopathy is characterized by maintained ATP delivery but reduced efficiency through substrate selection, while in DCM_{NW}, ATP supply is reduced.

The impact of stress on myocardial energetics in heart failure

When the workload of the normal heart is increased through cardiac pacing, the healthy myocardium increases glucose utilization,[19] oxygen consumption, and myocardial respiratory quotient, consistent with relatively increased carbohydrate oxidation. However, in heart failure, during cardiac pacing this substrate flexibility has been shown to be impaired.[20] As substrate selection is linked to ATP production, this may explain our observations here.

Normally, the capacity of the myocardium to continually generate energy through oxidative phosphorylation greatly exceeds demand, as is seen in the normal heart where PCr/ATP is not compromised with moderate increases in workload.[5] In this study, we observed that PCr/ATP remains stable and ATP delivery increases in the CTL_{NW} heart during stress. However, in both normal weight and obese heart failure groups, PCr/ATP fell with dobutamine stress, and CK flux remains static or falls, in DCM_{NW} and DCM_{OM} hearts, respectively. This suggests that myocardial ATP consumption outstrips supply, and the ability of CK to act as a temporal and spatial buffer for ATP is exceeded. As both DCM_{NW} and DCM_{OB} hearts are likely to be insulin resistant, heavily reliant on fatty acid oxidation at rest and having limited ability to alter substrate selection in response to demand, this may underlie the energetic changes seen here.

The more profound fall in stress ATP delivery in DCM_{OB} as compared to DCM_{NW} may be related to the induction of mitochondrial uncoupling proteins,[18] limiting the rate of ATP production to a greater extent in obesity than normal weight, with stress unmasking the deficit.

The impact of weight loss in heart failure

As DCM_{OB} were characterized by preserved resting ATP delivery through CK flux, which was not different to CTL_{NW} hearts, this suggests reduced myocardial efficiency in terms of work delivered per unit of energy. We have shown here that successful intentional weight loss in DCM_{OB} is accompanied by positive remodelling with reduced LV mass and reduced LV cavity size. In addition, LVEF was significantly improved, but interestingly ATP delivery rate through CK flux fell. This would suggest that myocardial efficiency was improved, and that this may contribute to improved systolic function. While LV stroke work did not change, the reduction in LV volumes indicates that LV wall stress would similarly reduce, as LV function is shifted to a more favourable position on the Frank–Starling curve.

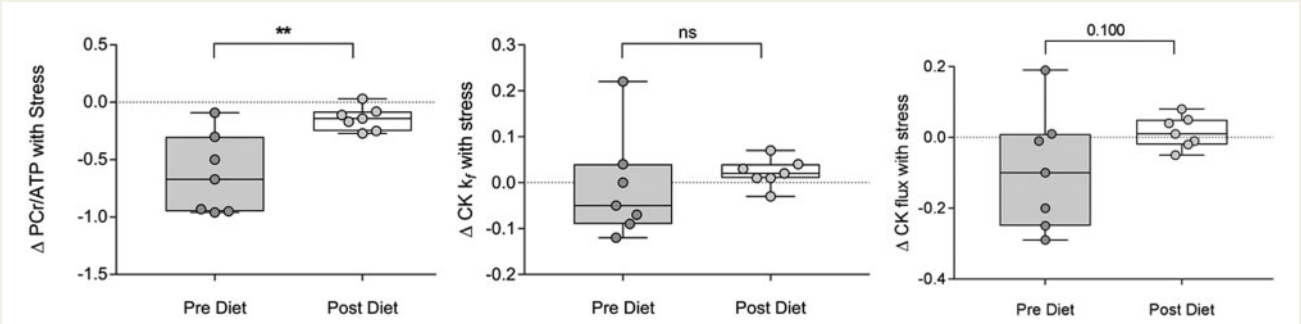


Figure 5 The effect of weight loss on stress cardiac energetics in obese patients with dilated cardiomyopathy. CK, creatine kinase; ns, non-significant; PCr/ATP, phosphocreatine to adenosine triphosphate ratio. **p<0.01.

This may also explain why energy demands on the myocardium fell in response to weight loss.

Albeit with small numbers and requiring validation, the return of stability of PCr/ATP and increase in ATP delivery through CK after weight loss to a pattern that is reflective of the normal heart, rather than the DCM_{NW} heart, is an interesting observation. This, as well as the observation that myocardial contractility improves with weight loss, would argue for the existence of a distinct obesity cardiomyopathy, where obesity drives altered myocardial energetics and cardiac dysfunction, and not merely the existence of an underlying DCM that is exacerbated by obesity.

The obesity paradox

Despite the fact that obesity is a key risk factor for developing heart failure,[21–23] there exists a paradoxical relationship between survival in established heart failure and BMI.[24] This suggests that increasing body size is associated with improved prognosis. Given the numerous physiological challenges invoked by increasing body fat mass and its metabolic complications, this is surprising and rather counterintuitive.

A number of potential explanations for this phenomenon exist,[25] including statistical bias on a population level and earlier presentation in obese individuals. However, one hypothesis is that there is a protective physiological process in obesity, which is beneficial in heart failure. This study raises the noteworthy question of whether the different energetic basis of heart failure in obesity seen in this study confers a favourable energetic state and a physiological basis for the obesity paradox, and this is worthy of further investigation.

Future directions

The management of obesity in the context of heart failure is a highly relevant problem in current clinical practice, and yet there is a paucity of quality evidence in the field. It is therefore not surprising that current clinical guidelines give no specific recommendations.[26,27] Given the existence of the obesity paradox, it is crucial that randomized prospective clinical studies of the management of obesity in heart failure, as well as any specific pathophysiological features of the condition such as have been elucidated in this study, are prioritized to tailor appropriate and effective management to this significant proportion of patients.

Limitations

While the clinical syndromes of heart failure and obesity affect millions of patients worldwide, we acknowledge that the technical complexity of the methods in this paper means that the cohorts recruited are both carefully selected and relatively small. Participants with cardiac devices were excluded; hence, the majority of participants had moderate rather than more severe heart failure. In addition, there was a degree of drop-out due to device implantation in keeping with expectations.

Weight loss, particularly in combination with heart failure, is difficult, and while only two-third of the obese cohort were successful in body fat reduction, we feel that this was in keeping with other studies even in the absence of heart failure. In addition, the clear impact on LV function even with a small sample size would suggest that it is a true reflection of the importance of weight management.

These results, particularly of the stress energetic response following weight loss, need to be borne out in larger scale trials, to establish the feasibility of targeting metabolic treatments to this patient group.

Conclusions

Myocardial ATP delivery rate through CK flux is reduced in normal weight individuals with DCM and is related to reduced systolic function. Despite similarly reduced systolic function, ATP delivery is higher in obese DCM and similar to healthy individuals, suggesting that a cause of dysfunction is reduced efficiency of energy utilization. Successful weight loss is accompanied by systolic recovery alongside reduced ATP delivery rate, suggesting that weight loss can improve myocardial energetic efficiency. Overall, this study supports the existence of a distinct obesity cardiomyopathy, that is characterized by reduced myocardial efficiency but maintained ATP delivery. It also highlights the importance of weight loss as a potential therapeutic intervention in patients with obesity and heart failure.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

All data available upon reasonable request to the corresponding author.

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