Adverse right ventricular remodelling, function, and stress responses in obesity: insights from cardiovascular magnetic resonance

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Aims
We aimed to determine the effect of increasing body weight upon right ventricular (RV) volumes, energetics, systolic function, and stress responses using cardiovascular magnetic resonance (CMR).

Methods and results
We first determined the effects of World Health Organization class III obesity [body mass index (BMI) > 40 kg/m2, n = 54] vs. healthy weight (BMI < 25 kg/m2, n = 49) upon RV volumes, energetics and systolic function using CMR. In less severe obesity (BMI 35 ± 5 kg/m2, n = 18) and healthy weight controls (BMI 21 ± 1 kg/m2, n = 9), we next performed CMR before and during dobutamine to evaluate RV stress response. A subgroup undergoing bariatric surgery (n = 37) were rescanned at median 1 year to determine the effects of weight loss. When compared with healthy weight, class III obesity was associated with adverse RV remodelling (17% RV end-diastolic volume increase, \(P<0.0001\)), impaired cardiac energetics (19% phosphocreatine to adenosine triphosphate ratio reduction, \(P<0.001\)), and reduction in RV ejection fraction (by 3%, \(P=0.01\)), which was related to impaired energetics (\(R=0.3, P=0.04\)). Participants with less severe obesity had impaired RV diastolic filling at rest and blunted RV systolic and diastolic responses to dobutamine compared with healthy weight. Surgical weight loss (34 ± 15 kg weight loss) was associated with improvement in RV end-diastolic volume (by 8%, \(P=0.006\)) and systolic function (by 2%, \(P=0.03\)).

Conclusion
Increasing body weight is associated with significant alterations in RV volumes, energetic, systolic function, and stress responses. Adverse RV modelling is mitigated with weight loss. Randomized trials are needed to determine whether intentional weight loss improves symptoms and outcomes in patients with obesity and heart failure.

Keywords
obesity • magnetic resonance • remodelling

Introduction
Obesity is associated with impaired exercise tolerance1 and a two-fold increased risk of developing heart failure,2 leading to declines in quality of life and life expectancy.3 The mechanisms by which obesity leads to impaired exercise tolerance4 and an increased risk of heart failure are incompletely understood but are of interest, especially as obesity is, in principle, a risk factor which could be modified via weight loss. The mechanisms linking obesity to the development of heart failure are incompletely understood but are likely to include adverse haemodynamic conditions due to an increased circulating volume,6 a dysregulated inflammatory state and impaired of left ventricular (LV) energy supply7 linked to altered substrate metabolism.8

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remodelling in obesity is known to include mild concentric hypertrophy and impairment of diastolic function, \( ^9 \) which might contribute to increases in pulmonary pressures both at rest and during exercise when symptoms are more likely to occur.

Right ventricular (RV) remodelling in obesity is less well studied than LV remodelling, but has been reported (in milder class I–II obesity classes at rest) to include subtle RV cavity dilatation and RV hypertrophy.\(^{10–12}\) Whether more severe RV modelling and overt systolic dysfunction occurs in more severe obesity (i.e. class III obesity, body mass index (BMI) > 40 kg/m\(^2\)) is unknown as the cardiovascular phenotype of class III obesity has not previously been specifically investigated. Whether obesity is also associated with an impaired response of the right ventricle to stress is also unknown.

To address these questions, we conducted clinical investigations in which we: (i) used cardiovascular magnetic resonance (CMR) to investigate RV remodelling and systolic function in patients with morbid (class III) obesity, (ii) documented RV systolic and diastolic functional reserve during catecholamine stress in less severe obesity using CMR, and (iii) investigated whether obesity-associated RV remodelling and dysfunction was reversible following weight loss.

## Methods

### Study participants

In total, 130 unique participants were included in this prospective investigation (Study 1, \( n = 103 \)) of whom \( n = 37 \) were rescanned for Study 3, and Study 2, \( n = 27 \).

### Study 1: Effects of class III obesity on RV morphology and function

The study received favourable ethical approval (17/SC/0167), and written informed consent was obtained from all 103 participants. The study participants were \( \geq 18 \) years of age and were able to give written informed consent to participate. Exclusion criteria included uncontrolled atrial fibrillation, history or symptoms of flow-limiting coronary artery disease, evidence of previous myocardial infarction, a diagnosis of type II diabetes requiring medication treatment, severe valvular heart disease, recent change in medications or BMI (within the preceding 3 months), and standard contraindications to magnetic resonance (MR) scanning (pregnancy, breastfeeding, implanted metallic devices, severe claustrophobia). All study visits were performed with the volunteer fasted for 8 h.

CMR scans for the assessment of ventricular function were performed using a 1.5T MR system; \(^{31}\)P-MRS was performed in a subgroup of participants at 3T. Detailed sequence and spectroscopic methods are provided below. Clinical and laboratory data were acquired during the study visit.

### Study 2: Investigating RV stress reserve in obesity

The study was ethically approved (05/Q1603/29) and written informed consent was obtained from all 27 participants (18 with obesity and 9 control participants of healthy weight). Inclusion and exclusion criteria were as for Study 1.

Following acquisition of a baseline short-axis cine magnetic resonance imaging stack at 1.5T, dobutamine was infused intravenously at incremental rates between 5 \( \mu \)g/kg/min and 40 \( \mu \)g/kg/min with a target of 65% of age maximal heart rate. During this time, blood pressure was measured every minute. Heart rate, blood pressure, pulse oximetry, and cardiac electrograph complex morphology were also monitored continuously during both of the dobutamine infusion studies. Heart rate was then maintained at target and a second short-axis stack obtained previously described.\(^{13}\) Consenting participants then underwent repeat examination on a different day for rest and stress \(^{31}\)P spectroscopic measurements (three participants in the control group and four participants in the obesity group did not undergo a further stress examination at 3T).

Analysis for right and LV volumes was performed using cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada). RV and LV short-axis slices were manually contoured from base to apex, to derive ventricular volumes and mass, and then the right ventricle was contoured across the entire cardiac cycle to generate RV volume-time curves. Diastolic peak filling rate and time to peak filling rate were derived as previously described.\(^{13}\)

### Study 3: Investigating the reversibility of adverse RV remodelling in class III obesity following surgical weight loss

To investigate the reversibility of RV remodelling in class III obesity, 37 of the participants recruited to Study 1 (ethical approval 17/SC/0167) underwent repeat CMR imaging at median 12 months (interquartile range (IQR) 8–14) following weight loss surgery which was performed as part of usual clinical care.

### CMR imaging at 1.5T

Images for ventricular volumes and diastolic function were acquired using a steady state free precession sequence with an echo time (TE) of 1.5 ms, a repetition time (TR) of 3.0 ms, in plane resolution 1.5 \( \times \) 1.5 mm\(^2\), temporal resolution 33.74 ms and a flip angle of 60\(^\circ\). All imaging was performed supine, was prospectively cardiac gated and acquired during end-expiratory breath hold.

### \(^{31}\)P magnetic resonance spectroscopy at 3T

All \(^{31}\)P spectra were acquired using a 3T Siemens MR system and were acquired in the fasting state. Subjects lay prone with the left ventricle centred over a modified heart/liver Siemens coil. A 3D acquisition-weighted chemical shift imaging (Chemical Shift Imaging CSI technique, TE = 0.3 ms) sequence was used, in conjunction with an optimised radiofrequency pulse centred between T and \( \nu \) resonances to maximise the signal to noise ratio, improve baseline artefacts and ensure uniform excitation of all spectral peaks. The acquisition matrix size was \( 16 \times 8 \times 8 \) mm, and the field of view was \( 240 \times 240 \times 200 \), with 12 averages at k-space centre. Nuclear Overhauser Enhancement was used to increase the signal to noise ratio. Proton localisation images were used to obtain short-axis LV planes. To minimise potential signal contamination, two saturation bands were placed over the anterior chest-wall skeletal muscle and one over the liver. The CSI grid was positioned on a slice designated as the first short-axis slice in which the papillary muscle became visible and rotated to obtain one voxel containing mid-ventricular septal myocardium. During analysis, all spectra were coded to exclude descriptive data, with voxels selected independently, and analysis completed prior to unblinding. Selected spectra were pre-processed (dispersion and baseline correction) and fitted using the automated processing algorithm (Advanced Method for Accurate, Robust and Efficient Spectral fitting) AMARES within the MRUI software packages. The quality of the spectral fit was assessed using the coefficient of variation in the measured PCR/ATP value based on the Cramer–Rao lower bounds. Spectra were determined to be sufficient quality if they had a coefficient of variation below 20%.

### Statistical methods

All statistics were analysed using a commercial software package (SPSS 22; SPSS, Chicago, IL, USA) or Graphpad Prism 8.4.2 (Graph Pad, San Diego, CA).
Diego, CA, USA). All data are presented as mean ± standard deviation unless otherwise stated as median (IQR). Normality of distribution was assessed before determination of statistical significance. Mann–Whitney U testing was used for non-normally distributed data and Student’s t-tests for normally distributed continuous data (paired or independent where appropriate). Correlations were assessed using Pearson R method. Values of P < 0.05 were considered statistically significant, all tests were two-sided.

Individual de-identified participant data can be made available upon requests directed to the corresponding author; after approval of a proposal, data can be shared through a secure online platform.

Results

Study 1: Effects of class III obesity on RV morphology and function

The cohort of participants living with class III obesity in the absence of major comorbidity (BMI > 40 kg/m², n = 54) had a mean cohort BMI of 46.5 ± 4 kg/m², compared to volunteers of healthy weight (BMI 18.5–24.9 kg/m², n = 49) who had a mean cohort BMI of 21.9 ± 2 kg/m². Participants with class III obesity had a mean 65 kg higher body mass, a mean 50 kg higher fat mass estimated using dual energy X-ray absorptiometry (DEXA) and were insulin resistant, with a two-fold increase in homeostatic model assessment of insulin resistance (HOMA-IR, P = 0.002, Table 1). The two groups were reasonably well matched for age, systolic blood pressure, diastolic blood pressure, and total cholesterol (Table 1).

When compared with participants of healthy weight, class III obesity was associated with remodelling of both the right and left ventricles (Figure 1). Class III obesity was associated with a 17% increase in RV end-diastolic volume (RVEDV 163 ± 30 mL vs. 139 ± 28 mL, P < 0.0001), a 26% increase in RV end-systolic volume (RVESV 71 ± 20 mL, P < 0.0001), and a 3% absolute reduction in RV ejection fraction (62 ± 6% vs. 65 ± 7%, P = 0.01). The differences in RVEDV and LV end-diastolic volume (LVEDV) remained highly statistically significant when indexing to the height allometric power 2.7 (indexed RVEDV 41 ± 833 ± 6 mL/m².7 vs. 33 ± 6 mL/m².7, P < 0.0001 and LVEDV 40 ± 633 ± 6 mL/m².7 vs. 33 ± 4 mL/m².7, P < 0.0001).

Using 31P spectroscopy at 3T to assess cardiac energetics, class III obesity was associated with a 19% reduction in the phosphocreatine to adenosine triphosphate (PCr/ATP) ratio, a key index of overall cardiac energetic status (from 2.1 ± 0.3 to 1.7 ± 0.4 at rest, P = 0.0002, Figure 1). This energetic deficit was linked to the reduction in RV systolic function (R = 0.30, P = 0.04, Figure 1).

Participants with class III obesity had a 12% increase in LVEDV (155 ± 30 mL vs. 139 ± 23 mL, P = 0.003) and a 24% increase in LV mass (125 ± 24 g vs. 101 ± 25 g, P < 0.0001), reflecting a combination of eccentric and concentric remodelling. LV systolic function was assessed by both the short-axis CMR derived LV ejection fraction (LVEF) and by systolic circumferential strain analysis using feature tracking and was not different in obesity (LVEF 67 ± 6% vs. 67 ± 6%, P = ns). Obesity was however associated with a 9% reduction in peak LV diastolic strain rate (P < 0.05) and a 17% increase in left atrial volume (83 ± 23 mL vs. 71 ± 20 mL, P = 0.007), both suggestive of LV diastolic dysfunction.

Collectively these findings establish that the cardiac phenotype of class III obesity includes dilatation of both the right and left ventricles and mild RV systolic dysfunction at rest which is linked to energetic impairment. These findings motivated us to analyse RV responses during dobutamine stress in patients with less severe obesity, to determine whether subclinical RV dysfunction could be unmasked prior to the development of overt remodelling at rest.

Study 2: Investigating RV stress reserve in obesity

The study included 18 participants with predominantly class I–II obesity (mean BMI 35 ± 5 kg/m²) and 9 control participants of healthy

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics for class III obesity and healthy weight study participants</th>
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<tbody>
<tr>
<td>Healthy weight BMI 18–24.9 kg/m² (N = 49)</td>
<td>Obesity class III BMI &gt;40 kg/m² (N = 54)</td>
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<tr>
<td>Age, years</td>
<td>42 ± 15</td>
</tr>
<tr>
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<td>Weight, kg</td>
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</tr>
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<td>BMI, kg/m²</td>
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<td>Systolic BP, mmHg</td>
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<tr>
<td>Diastolic BP, mmHg</td>
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</tr>
<tr>
<td>Fat mass total, kg</td>
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<tr>
<td>Visceral fat abdominal, cm²</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
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<tr>
<td>Fasting triglycerides, mmol/L</td>
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</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
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</tr>
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<td>Fasting insulin, mIU/L</td>
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<td>HOMA-IR</td>
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</table>

Data are presented as mean ± standard deviation.

BMI, body mass index; BP, blood pressure; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; NA, Not applicable.
weight (BMI 22 ± 1 kg/m², Figure 2) who underwent cine imaging covering the entire right ventricle before and during dobutamine stress. Baseline characteristics of the participants are presented in Table 2.

At rest, obesity was associated with a prolonged time to onset of peak RV filling rate from end-systole (from 148 ± 29 to 202 ± 31 ms, $P < 0.001$, Figure 2) suggestive of RV diastolic dysfunction. Dobutamine infusion led to a mean 59% increase in heart rate (from 66 ± 9 bpm to 104 ± 13 bpm across all participants) which was not significantly different between obesity and healthy weight (mean increase in heart rate 40 ± 7 vs. 34 ± 17 bpm, $P = \text{ns}$).

Participants of healthy weight had a 19 ± 3% absolute increase in RV ejection fraction during dobutamine stress, which was significantly attenuated to a 12 ± 8% absolute increase in obesity ($P = 0.004$, Figure 2). This finding is consistent with impaired RV systolic contractile response to dobutamine. The stress inducible change in peak RV filling rate was also significantly reduced (from 2.1 ± 1 mL/s to 0.5 ± 1 mL/s, $P < 0.05$, $* * * P < 0.001$). Hollow circles denote participants with healthy weight, black circles those with class III obesity.

Figure 1 Cardiac phenotype in class III obesity assessed using CMR. (A) Participants of healthy weight and with class III obesity underwent 1.5T and 3T CMR and a subgroup underwent $^{31}$P MRS. (B) Assessment of cardiac volumes and systolic function using CMR (red—LV endocardium, green—LV epicardium, orange—left atrium, and yellow—right ventricular endocardium) including feature tracking strain analysis and representative $^{31}$P spectrum. (C) Class III obesity was associated with RV dilatation and systolic dysfunction which was associated with impairment of cardiac energetics. (D) Class III obesity was associated with LV remodelling and impairment of systolic but not diastolic function. Unless otherwise stated data are presented as mean ± standard deviation, $* P < 0.05$, $* * P < 0.01$, $* * * P < 0.001$. Hollow circles denote participants with healthy weight, black circles those with class III obesity.
Abnormal RV systolic and diastolic stress response in obesity. Study participants (n = 27) with class I–II obesity or healthy weight underwent cine CMR before and during dobutamine stress; a subgroup also underwent $^{31}$P MRS for energetics. Participants with obesity had a delayed peak of diastolic RV filling at rest consistent with diastolic dysfunction, an attenuated stress inducible increase in RV ejection fraction, and an impaired stress inducible change in peak RV filling rate (a measure of stress RV diastolic dysfunction). There was a non-significant numerical trend to greater cardiac energetic deficit during stress in obesity. Data are presented as mean ± standard deviation, *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Table 2  Baseline characteristics for RV dobutamine stress response study participants

<table>
<thead>
<tr>
<th></th>
<th>Healthy weight BMI 18.5–24.9 kg/m² (n = 9)</th>
<th>Obesity BMI &gt;30 kg/m² (n = 18)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>40 ± 9</td>
<td>47 ± 9</td>
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<tr>
<td>Height, cm</td>
<td>168 ± 6</td>
<td>168 ± 10</td>
<td>0.94</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60 ± 6</td>
<td>97 ± 15</td>
<td>&lt;0.001</td>
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<tr>
<td>BMI, kg/m²</td>
<td>22 ± 1</td>
<td>35 ± 5</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>111 ± 10</td>
<td>108 ± 27</td>
<td>0.08</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>70 ± 10</td>
<td>74 ± 6</td>
<td>0.08</td>
</tr>
<tr>
<td>Fat mass total, kg</td>
<td>19.6 ± 9</td>
<td>49.1 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.9 ± 0.7</td>
<td>5.4 ± 2.2</td>
<td>0.18</td>
</tr>
<tr>
<td>Fasting triglycerides, mmol/L</td>
<td>0.8 ± 1</td>
<td>1.3 ± 1</td>
<td>0.04</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.7 (4.6–5.0)</td>
<td>5.2 (4.6–5.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>0 (0–0)</td>
<td>0.1 (0–0.7)</td>
<td>0.07</td>
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<tr>
<td>Interleukin 6, ng/mL</td>
<td>1.8 (0–4.0)</td>
<td>5.9 (1.0–8.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Fasting Insulin, mIU/L</td>
<td>2.1 ± 2</td>
<td>8.4 ± 6</td>
<td>0.01</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>30 ± 30</td>
<td>91 ± 60</td>
<td>0.12</td>
</tr>
<tr>
<td>Non-esterified fatty acids, mmol/L</td>
<td>0.6 ± 0.4</td>
<td>0.4 ± 0.3</td>
<td>0.15</td>
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</tbody>
</table>

Data are presented as mean ± standard deviation or median (IQR). BMI, body mass index; BP, blood pressure.
P = 0.008), suggesting an impaired stress RV diastolic functional reserve.

We explored candidate mechanisms linking obesity to impaired RV stress responses. During stress, there was a non-significant numerical trend to further reduction in cardiac energetics assessed using PCr/ATP ratio in obesity (P = 0.06, Figure 2). There was no association between stress inducible change in peak RV filling rate and C-reactive protein (R = 0.27, P = ns), although there was a trend for association with IL-6 (R = 0.45, P = 0.05) which is the cytokine most clearly linked to excess visceral adipose tissue. There was an association with serum insulin level (R = 0.65, P < 0.001) but not leptin (R = 0.44, P = ns) nor non-esterified fatty acid concentration (R = 0.13, P = ns). The association between insulin level (and correlational trend with IL-6) and RV diastolic stress response are hypothesis-generating but may suggest that metabolic, energetic and inflammatory mechanisms link obesity to changes in RV function.

Overall, these findings are consistent with significantly abnormal RV stress responses in class I–II obesity, prior to the development of overt resting changes observed in class III obesity.

Study 3: Investigating the reversibility of adverse RV remodelling in class III obesity following surgical weight loss

We next investigated whether RV remodelling and systolic impairment in class III obesity might be reversible. Participants with class III obesity (n = 37) who were included in Study 1 were rescanned at median 12 months (IQR 8–14) following clinically indicated weight loss surgery (Figure 3).

Weight loss surgery led to a mean 32 ± 16 kg weight loss at 1 year. Weight loss was associated with a reduction in RV cavity size (RVEDV 160 ± 27 mL vs 147 ± 23 mL, P = 0.006), and an improvement in RV systolic function (RVEF 62 ± 6% vs 64 ± 6%, P = 0.026, RVEF 55 ± 15 mL vs 61 ± 16.0 mL, P = 0.03) despite an expected reduction in RV stroke volume (99 ± 18 mL vs 94 ± 14 mL, P = 0.04). Although underpowered and not statistically significant (with only 12 of the cohort having undergone repeat 31P spectroscopy), there was a numerical trend towards improvement of cardiac energetics following weight loss surgery with a ∼10% increase in PCr/ATP ratio (P = 0.13).

Collectively, these findings suggest that obesity-related RV remodelling and impairment of systolic function can both be improved following weight loss.

Discussion

In participants free from additional major comorbidities, class III obesity was associated with RV dilation and a modest reduction in the RV ejection fraction at rest, along with LV dilatation and diastolic dysfunction without impairment of LV systolic function. Participants with less severe obesity had preserved RV systolic function at rest though demonstrated impairment of RV systolic and diastolic responses to dobutamine stress when compared with people of healthy weight. In participants with class III obesity, surgical weight loss was associated with improvement in both RV dilatation and RV ejection fraction.

Collectively, these observations suggest that RV modelling, dysfunction and impairment of contractile reserve are under-recognized components of the obesity syndrome; impairment of RV systolic function at rest is not reported in less severe obesity classes. Although the absolute changes in RV systolic function observed at rest in this study are apparently subclinical at rest (with an absolute change in RVEF of -3%), the significant degree of RV dilatation as well as the marked reduction of stress reserve suggest that these findings may become more clinically significant in patients with obesity who develop acute or chronic disorders which stress the right ventricle.

The right ventricle is known to be more afterload-sensitive than the left ventricle, rendering it susceptible to pulmonary hypertension, and these deficits in RV reserve in obesity are likely to further impair the ability to augment pulmonary blood flow during exercise (when symptoms are most likely to occur) and when additional disorders stressing the RV occur (e.g. acute respiratory illness or pulmonary thromboembolic disease). This is in turn likely to promote systemic venous congestion, impairing function of other organs upstream of the right heart, including the kidneys and gut and providing possible mechanisms by which obesity is associated with adverse clinical outcomes in disorders stressing the right ventricle.

We show potential for weight loss to improve RV dimensions and systolic function in severe obesity,19 suggesting that obesity is a modifiable risk factor for RV dysfunction. International guidelines generally do not currently advocate intentional weight loss for patients with obesity and heart failure,20 reflecting the so-called ‘obesity paradox’ in which obesity is associated with an increased risk of developing heart failure but a reduced risk of adverse outcome in established heart failure.21,22 Whilst it remains unclear whether the obesity paradox reflects residual confounding or a true protective effect of obesity, a growing body of evidence has separately established that intentional weight loss via dietary or surgical means is associated with improved indices of cardiac structure and function and the incidence of heart failure.23 These data complement existing studies showing potential for weight loss to improve LV function24 and suggest that RV unloading through weight loss may therefore be a strategy which could be tested to improve exercise tolerance and reduce the risk of developing heart failure in obesity. Randomised controlled trials of intentional weight loss in heart failure are now warranted.

Limitations

Cardiac energetic assessment in our study was conducted using a voxel placed in the interventricular septum, as techniques to allow reliable quantitation of high energy phosphorus molecules localised to the right ventricle are not currently available, though this may be possible with future ultra-high field magnetic resonance techniques. Right heart catheterisation was not performed as part of the research protocol as the risks from invasive assessment could not be justified at this stage. No participant in this study had a diagnosis of pulmonary hypertension and no participant took pulmonary vasodilator therapy.

Conclusion

Increasing body weight is associated with RV remodelling, impaired cardiac energetics, and RV systolic dysfunction at rest, whilst less severe obesity is associated with impaired RV stress responses prior to the development of overt dysfunction. Obesity-related RV remodelling and systolic dysfunction are mitigated following weight loss.
Obesity-related RV remodelling and dysfunction is a modifiable component of the obesity syndrome which may have relevance to acute and chronic disorders stressing the right heart.

**Data availability**

De-identified data can be made available upon request directed to the corresponding author; after approval of a proposal, data can be shared through a secure online platform.

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**Conflict of interest:** none declared.

**References**