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CEST MRI reveals a correlation between visceral fat mass and reduced myocardial creatine in obese individuals despite preserved ventricular structure and function

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Abstract

Systolic cardiac function is typically preserved in obese adults, potentially masking underlying declines in cardiomyocyte metabolism that may contribute to heart failure. We used chemical exchange saturation transfer (CEST) magnetic resonance imaging (MRI), a sensitive method for measurement of myocardial creatine, to examine whether myocardial creatine levels correlate with cardiac structure, contractile function, or visceral fat mass in obese adults. In this study, obese (BMI > 30, n = 20) and healthy (BMI < 25, n = 11) adults were examined with dual-energy x-ray absorptiometry to quantify fat masses. Cine MRI and myocardial tagging was performed at 1.5T to measure ventricular structure and global function. CEST imaging with offsets ranging from ± 10 ppm were performed in one mid-ventricular slice, where creatine CEST contrast was calculated at 1.8ppm following field homogeneity correction. Ventricular structure, global function (Ejection Fraction: $69.4 \pm 4.3\%$ Healthy vs $69.6 \pm 9.3\%$ Obese, NS), and circumferential strain ($-17.0 \pm 2.3\%$ Healthy vs $-16.5 \pm 1.5\%$ Obese, NS) and strain rate were preserved in obese adults. However, creatine CEST contrast was significantly reduced in obese adults ($6.8 \pm 1.3\%$ Healthy vs $4.1 \pm 2.7\%$ Obese, $p=0.001$). Creatine CEST contrast was inversely correlated with total body fat% ($\rho = -0.45$, $p=0.011$), visceral fat mass ($\rho = -0.58$, $p=0.001$) and septal wall thickness ($\rho = -0.44$, $p=0.013$), but uncorrelated to ventricular function or contractile function. In conclusion, creatine CEST-MRI reveals a strong correlation between heightened body and visceral fat masses and reduced myocardial metabolic function that is independent of ventricular structure and global function in obese adults.

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Disclosure

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Graphical Abstract

Obese adults are at significantly higher risk of developing heart disease characterized by preserved function. Changes in underlying metabolic function is believed to occur over years prior to functional decline. We used cardiac chemical exchange saturation transfer (CEST) MRI to map myocardial creatine as a metabolic marker in obese adults. Creatine CEST contrast was significantly reduced in obese adults compared to healthy controls, and creatine reduction was inversely correlated with body and visceral fat contents.

Keywords

Creatine; CEST MRI; cardiac; obesity; metabolism

Introduction

Obese adults are at significantly higher risk of developing heart disease characterized by preserved systolic function,^{1,2} left ventricular (LV) hypertrophy, and increased end diastolic volume.³ However, while declines in ventricular function often manifest at late stages of heart failure in obese adults, changes in underlying metabolic function and substrate utilization are believed to occur over years prior to functional decline.^{3–5} The creatine kinase (CK) system plays an essential role within cardiomyocytes in regulating energy metabolism via the controlled transfer, buffering and utilization of high energy phosphates from adenosine triphosphate (ATP).⁶ Previous studies have consistently shown reduced CK system metabolites including ATP, phospho-creatine (PCr), and creatine across several pathologies of heart failure^{6–11}, primarily via measurement of either reduced PCr-to-ATP ratio or rate of ATP synthesis through CK flux using ³¹P magnetic resonance spectroscopy (MRS). Reductions in PCr-to-ATP ratio have been demonstrated in patients with ischemic heart disease,^{12,13} heart failure with reduced^{14,15} or preserved ejection fraction,¹⁶ and hypertrophic cardiomyopathy.^{17,18} Similarly, decreased myocardial creatine content has

been shown using ^1H MRS in both dilated and hypertrophic cardiomyopathy,¹⁹ and a number of other non-ischemic cardiomyopathies.²⁰ Obese adults with no history of cardiovascular diseases have demonstrated attenuated PCr-to-ATP ratios across multiple studies,^{3,21,22} as have healthy adults after brief exposure to a high fat diet.²³ Importantly, examination of cardiac metabolism in the setting of obesity can provide further insight into early pathological processes that may precede structural or functional changes of the LV. However, the use of a single large voxel, specialized radiofrequency coils, and long scan times have limited the clinical application of MRS for this purpose.

Chemical exchange saturation transfer (CEST) magnetic resonance imaging (MRI) is an emerging method for *in vivo* imaging of endogenous metabolites²⁴ including creatine via targeting of the labile amine ($-\text{NH}_2$) protons.²⁵ CEST-MRI exploits the exchange of magnetization from protons that resonate at frequencies offset from water (e.g. amine protons resonate at 1.8ppm) and undergo exchange with surrounding bulk water at an intermediate rate. Irradiation with RF energy tuned to the target resonant frequency saturates the magnetic moment, which is then transferred to the bulk water pool through chemical exchange, and detected as a loss in signal. In contrast to MRS methods, differences in saturation frequencies and exchange rates between creatine and other metabolites of the CK system enable selective contrast generation from creatine alone.^{25,26} In addition, CEST enables imaging with higher sensitivity to creatine concentrations as compared to MRS techniques^{27,28} and can be performed with standard hardware. CEST imaging of myocardial creatine has been performed in infarcted large animal models^{28,29} and one patient with chronic myocardial infarction,²⁹ with both studies revealing significantly reduced creatine CEST in infarcted tissue. In a prior study from our group, we observed attenuated cardiac creatine CEST contrast in obese mice fed a high fat diet despite preserved ventricular structure and systolic function.³⁰ In this study, we used cardiac CEST MRI of myocardial creatine, cine cardiac MRI, and myocardial tagging in obese and healthy adults to examine whether myocardial creatine CEST contrast is reduced in obese adults with preserved cardiac structure and function.

Methods

Participants and recruitment

Obese (body mass index (BMI) $> 30 \text{ kg/m}^2$, $n = 20$) and healthy (BMI $< 25 \text{ kg/m}^2$, $n = 11$) volunteers aged twenty-five to forty years old were recruited. Exclusion criteria included arrhythmia, known cardiovascular disease, renal disease, diabetes, tobacco use, history of chemotherapy, and standard MRI safety and compatibility concerns. Participants completed 12-lead electrocardiogram and hemoglobin A1c upon consent to confirm exclusion criteria. The research protocol was approved by the Institutional Review Board and all participants provided voluntary informed consent.

Imaging protocol

Total body fat percentage, visceral fat mass, and BMI were calculated by dual-energy X-ray absorptiometry (DXA) using a Lunar iDXA scanner (GE-Healthcare, Madison, WI, USA). A twelve-lead electrocardiogram was acquired to confirm the absence of arrhythmias.

Cardiac MRI was performed on a 1.5T Siemens Aera scanner (Siemens Healthcare, Erlangen, Germany) using a sixteen-channel body coil combined with a twelve-channel posterior coil. A 4-chamber long axis cine was acquired followed by a short axis stack of balanced steady state free precision cine images (8–11 slices, FOV $350 \times 350 \text{ mm}^2$, matrix size 256×192 , resolution $1.37 \times 1.37 \times 8 \text{ mm}^3$, 25 cardiac phases, number of averages = 1, TR/TE = 3.2/1.2 ms, flip angle 50°) across the span of the LV. Next, myocardial tagging was performed in one mid-ventricular short axis slice (FOV $340 \times 276 \text{ mm}^2$, matrix size 256×141 , resolution $1.33 \times 1.33 \times 8 \text{ mm}^3$, 12–25 cardiac phases, number of averages = 1, TR/TE = 8.3/3.9 ms, flip angle: 14° , tag spacing: 8mm). Finally, a series of 40 cardiac CEST images were acquired in the same slice. CEST preparation was performed using a train of five Gaussian-shaped pulses (flip angle of 320° , pulse duration of 25 ms, inter-pulse delay of 25 ms) with peak power of $0.5 \mu\text{T}$ and total saturation time of 250 ms. A segmented gradient recalled echo sequence was used to acquire a single cardiac phase during diastasis (FOV $350 \times 285 \text{ mm}^2$, matrix size 192×120 , resolution $1.82 \times 1.82 \times 8 \text{ mm}$, number of averages = 2, number of shots/segments 10/12, TR/TE = 6.4/2.9 ms, flip angle 35°). Images were acquired following saturation at offset frequencies of $-10, -3.6, -3.4, -3.2, -3.0, -2.8, -2.6, -2.4, -2.2, -2.0, -1.8, -1.6, -1.4, -1.2, -1.0, -0.8, -0.6, -0.4, -0.2, 0.0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6$, and 10 ppm. In addition, a reference scan was acquired with peak RF amplitude of $0.001 \mu\text{T}$. Each CEST scan (offset frequency) was performed in a single 15-second breath hold (40 breath-holds total). The total scan time for all imaging sequences was approximately 35 minutes.

Analysis of ventricular structure, function, and contractile function

LV end diastolic and systolic volumes, stroke volume, ejection fraction, cardiac output, and myocardial mass were calculated from cine images using Argus Viewer (Siemens Healthcare, Erlangen, Germany). In addition, ventricular volumes and mass were normalized to body surface area (BSA). Additional normalization to $\text{height}^2.7$, and ideal body mass was performed for supplementary analysis (as described in the supplemental data). Global longitudinal strain was derived from four chamber cine images using RadiAnt Dicom viewer v4.1 (Medixant, Poznan, Poland). Longitudinal strain waveforms were derived from changes in the length of the left ventricle. Peak global longitudinal strain was assessed at the end systolic phase. Longitudinal systolic and diastolic strain rates were calculated as the rates of longitudinal shortening and lengthening, respectively. Finally, peak circumferential strain and systolic circumferential strain rate were derived from myocardial tagging images using harmonic phase (HARP) analysis (Myocardial Solutions, Morrisville, NC, USA).

Cardiac CEST imaging analysis

All image processing was conducted offline using MATLAB version 2017b (The MathWorks Inc., Natick, MA, USA) using a custom algorithm. For each CEST image, a region of interest was defined to encompass the interventricular septum. The mean signal intensity at each offset was then normalized to the corresponding reference scan signal intensity, and water saturation shift referencing (WASSR) was applied on the resulting Z-spectrum to correct for B_0 field inhomogeneity.³¹ Creatine CEST contrast was quantified as the asymmetric magnetization transfer ratio (MTR_{asym}) as $\text{MTR}_{\text{asym}} = (S_{-1.8\text{ppm}} - S_{1.8\text{ppm}}) \times$

100(%) where S represents the mean normalized signal intensity at corresponding WASSR corrected offset.²⁵

Statistical analysis

Statistical results were computed using IBM SPSS Statistics Version 24 (IBM Corp, Armonk, NY, USA) and Microsoft Excel 2016. A Shapiro-Wilk test in SPSS was used to assess normality and homogeneity of variance of the acquired LV structural, functional, contractile function, and creatine CEST contrast measures. Participant groups were compared in Excel using a two tailed t-test. Creatine CEST contrast was correlated with body fat percentage, BMI, and all measures of ventricular structure and function using Pearson's correlations and linear regression tests in Excel. Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables are presented as count (%), where appropriate. $P < 0.05$ was considered significant for all tests.

Results

Groups were well matched in age and gender, all participants were in sinus rhythm, and obese adults demonstrated significantly higher BMI and total body fat percentage (Table 1). Obese adults demonstrated preserved ventricular end diastolic and systolic volumes and stroke volume (Table 2). While end diastolic volume index (EDVI) was significantly higher in obese adults, all values were within an established normal range for EDVI.³² Both septal wall thickness and the ventricular mass to volume ratio trended strongly higher in obese adults (Table 2), however LV mass index was not significantly different between healthy and obese adults when indexed to total BSA (Table 2). When indexed to height or ideal body mass, LV mass was significantly elevated in obese adults (Supplementary data Table S1). Resting heart rates and cardiac output were significantly higher in obese adults, however, when indexed to BSA, cardiac output was not significantly different from healthy controls (Table 2). Finally, ejection fraction was not significantly different between obese and healthy adults (Table 2).

Contractile Function

Both longitudinal and circumferential contractile function was preserved in obese adults. Representative global longitudinal strain waveforms from a healthy and obese adult are shown in Figure 1a. Peak global longitudinal shortening ($-21.8 \pm 2.4\%$ Healthy vs. $-21.7 \pm 1.9\%$ Obese, $p = 0.90$), and both systolic ($-83.8 \pm 14.4\%$ Healthy vs $-89.3 \pm 14.8\%$ Obese, $p = 0.32$), and diastolic ($148.5 \pm 32.9\%$ Healthy vs $133.1 \pm 35.5\%$ Obese, $p = 0.24$) strain rates were not significantly different among obese and healthy adults (Fig. 1). Sample myocardial tagging images are shown in Figure 2a. Both peak circumferential strain ($-17.0 \pm 2.3\%$ Healthy vs $-16.5 \pm 1.5\%$ Obese, $p = 0.51$) and systolic circumferential strain rate ($-85.7 \pm 14.8\%$ Healthy vs $-88.7 \pm 14.6\%$ Obese, $p = 0.58$) were not significantly different between both groups (Fig. 2).

Creatine CEST

Representative CEST images acquired without CEST-weighting, with CEST-preparation at the offset frequency of creatine (1.8ppm), and with CEST-preparation at the resonant

frequency of water are shown in Figure 3. Uniform signal saturation is observed in the septum, whereas inhomogeneity of both the B0 and B1 fields lead to variable saturation in the left ventricular free wall. Representative Z-spectra, and corresponding MTR_{asym} spectra, generated from septal regions of interest across all offset frequencies are presented in Figure 4. Mean creatine CEST contrast was significantly reduced in obese adults ($6.8 \pm 1.3\%$ Healthy vs $4.1 \pm 2.7\%$ Obese, $p=0.001$, Fig. 4).

Creatine CEST contrast inversely correlated with total body fat percentage, and strongly correlates with visceral fat mass (Fig. 5). Increasing BMI correlated with reduced creatine CEST contrast across all participants (Table 3). Interestingly, while creatine CEST contrast did not correlate with LV mass indexed to BSA (Table 3), a strong correlation was observed with septal wall thickness (Fig. 5) and ventricular mass indexed to height and ideal body weight. In parallel, we observed a strong correlation between increased cardiac output and reduced creatine CEST contrast (Table 3), however when corrected for BSA there was no correlation between cardiac output index and creatine CEST contrast (Table 3). Creatine CEST contrast did not correlate with functional parameters including ejection fraction (Table 3), peak circumferential strain (Fig. 6), circumferential strain rate (Table 3), longitudinal strain (Fig. 6), longitudinal strain rates whether diastolic (Fig. 6) or systolic (Table 3). Identical results were obtained when comparing creatine CEST contrast to circumferential strain and strain rate values obtained only in the septum (Table 3).

Discussion

Prior studies of obese adults have established preservation of systolic function despite higher risk of heart failure.^{2,33} In this context, changes in cardiomyocyte metabolism are emerging as an early underlying mechanism in the pathological cascade.^{3,5} In this study we implemented a cardiac CEST-MRI method to probe changes in myocardial creatine levels in the setting of adult obesity. The results of this study reveal reduced myocardial creatine in obese adults with preserved cardiac structure, global ventricular function, and contractile function. Reduced creatine was correlated with both increased septal wall thickness and visceral fat mass. Such findings reveal that creatine CEST-MRI may provide insight as an investigative tool in important questions surrounding mechanisms of heart failure in obesity.

Imaging of tissue creatine levels by CEST-MRI has previously been performed in both skeletal and cardiac muscle. In a pair of human studies of skeletal muscle energetics by Kogan et al,^{26,34} changes in creatine CEST contrast in response to an exercise challenge correlated with phosphocreatine recovery kinetics measured using ³¹P-MRS. Importantly, Harris et al²⁸ also demonstrated that CEST contrast generated at 1.8ppm in the heart reflects underlying creatine levels, not phosphocreatine or total creatine in large animal models. In the infarcted myocardium of large animals, resting creatine CEST contrast has been shown to be reduced by 50–70% compared to remote healthy myocardium.^{28,29} While the reduction in creatine CEST contrast among obese adults in this study was below that observed in infarcted tissue in prior studies, it closely resembled the relative reduction in creatine CEST contrast in border zone tissue seen in miniature pigs by Zhou et al.²⁹ However, the CEST contrast values measured in healthy controls in our study were lower than those observed in healthy myocardium in both prior studies, despite similar

cardiomyocyte creatine concentrations between species. It is important to note differences in how the CEST-weighted images were acquired between studies. In both prior animal studies, substantially higher peak radiofrequency power at higher static field strengths (3T) were used to generate CEST contrast as compared to the current study. At a lower field strength of 1.5T, our preliminary experiments revealed that use of high power both led to greater indirect saturation of water, and to significant regional B1 inhomogeneity. Further, models of creatine CEST exchange predict a reduction in creatine CEST contrast at higher peak saturation powers, which led us to use a lower saturation power.³⁵ For imaging at 1.5T, a two pool Bloch equation model (Fig. S4) revealed that use of peak B1 powers above 0.5 μ T leads to greater indirect water saturation and a reduction in creatine CEST contrast. Also, both prior studies were performed at field strengths of 3T (vs. 1.5T in the current study) using single-shot acquisitions. In the study performed by Zhou et al. the use of single-shot readouts enabled multiple points along a Z-spectrum to be acquired in a single breath hold.²⁹ In our preliminary studies, we observed significant motion artifacts when using a single-shot readout to acquire an end-diastolic frame, even when using a centric-out encoding scheme. Importantly, if images are acquired serially with CEST preparation incremented from negative to positive offset frequencies in a single breath-hold, then a bias at low positive offset frequencies may exist as the saturated myocardial magnetic moment following CEST preparation at 0ppm results in lower steady state signal of subsequent images. The use of a distinct breath-hold for each point along a Z-spectrum, coupled with the lower field strength and lower saturation power, may have allowed for more complete T1-relaxation of myocardium between offset frequencies than prior studies. Subsequently, lower creatine CEST contrast in our study may be more reflective of underlying methodological differences than meaningful differences in cardiomyocyte creatine content between studies.

Prior studies that examined changes in cardiac energetics in the setting of adult obesity have typically utilized MRS to quantify changes in the PCr-to-ATP ratio. In a study by Rider et al,³ obese subjects who demonstrated attenuated PCr-to-ATP ratios also demonstrated reduced peak diastolic filling rates compared to healthy controls. Both the PCr-to-ATP ratio and peak diastolic filling rates were further reduced under dobutamine stress. Interestingly, in a subsequent study by the same group, obese adults who underwent successful weight loss demonstrated improved PCr-to-ATP ratios that aligned with values from healthy controls. However, peak diastolic filling rates only partially recovered to healthy levels.²¹ The results of the current study agree with the aforementioned studies in finding no change in systolic global LV function or contractile function, or correlation with creatine levels among obese adults. However, unlike prior studies we did not observe a correlation between creatine levels and longitudinal diastolic strain rate. Separately, several studies have probed whether LV hypertrophy correlates with changes in the PCr-to-ATP ratio. In a study by Perseghin et al., healthy males with BMI ranging from 19 to 35 kg/m² demonstrated decreased PCr-to-ATP ratio as a function of increasing LV mass.²² Similar findings were observed in hypertrophic cardiomyopathy patients.¹⁸ We did not observe any correlation between creatine CEST contrast and LV mass when indexed to BSA. However, we observed strong correlations between creatine CEST contrast and LV mass when indexed to either height to the power of 2.7 or to ideal body weight.

The role of adiposity in promoting changes in myocardial metabolism in obese adults has been examined previously by comparing the PCr-to-ATP ratio to indexes including BMI and total body fat.^{3,22} While we did not observe a correlation between creatine CEST contrast and these indexes, we observed a significant correlation with visceral fat mass. In a prior study by Gaborit et al. both visceral and epicardial fat mass correlated with myocardial triglyceride content in obese adults.³⁶ Further, increased myocardial triglyceride content has been linked to cardiomyocyte remodeling, mitochondrial damage and cardiac dysfunction.^{37,38} Whether there exists a critical threshold of visceral fat mass that triggers metabolic changes in the heart can be examined in larger future studies.

In initiating this study, we sought to develop cardiac creatine CEST-MRI for human subjects. However, there are limitations to the current study that need to be addressed for future application to the investigation of metabolic changes in obesity. First, this study involved small group sizes which, given heterogeneity among obese adults, may have left analysis of correlations between creatine CEST contrast and some structural and functional parameters underpowered to find differences that may have existed. Second, participants' diet history, duration of obesity, and hemodynamic parameters including blood pressure were not assessed. Inclusion of such parameters is necessary to further understand the complex interactions between fat distribution patterns, body size parameters, hemodynamic alterations and cardiomyocyte metabolism. Third, ventricular diastolic function is typically assessed using echocardiography by measurement of the mitral annular velocity (ϵ) and peak velocity flow wave (E).³⁹ We did not have access to echocardiography instrumentation at the time, inclusion of such data may have revealed a correlation between reduced creatine CEST contrast and attenuated diastolic function as observed in prior studies that used MRS. Fourth, while we chose to acquire one CEST-weighted image per breath hold for the aforementioned reasons, this resulted in long acquisition times to acquire a reasonably sampled Z-spectrum. While the use of multiple breath holds increases the likelihood of inter-breath hold motion, the average Dice coefficient for the segmented heart at each offset frequency relative to the reference image was 0.90 ± 0.06 , with most individuals showing a maximum shift of 3 voxels in any direction between breath-holds. Furthermore, both B0 and B1 inhomogeneity at the LV free wall limited the application of this method to the ventricular septum. B0 inhomogeneity can be addressed retrospectively using WASSR correction if sufficient spectral sampling occurred during acquisition of CEST-weighted images. However, since CEST contrast generation is a function of B1 (see Supplemental Fig. 4), correction for B1 inhomogeneity requires the use of more complicated analysis approaches. In this regard, the field strength at which cardiac CEST imaging is performed offers competing trade-offs. While a move to higher field strengths (3T and 7T) increases the amine labeling efficiency due to accelerated exchange rates, B0 inhomogeneity increases in parallel. In addition, significantly higher B1 power is required to maximize CEST contrast from creatine at higher field strengths, leading to a greater confounding influence of B1 inhomogeneity and magnetization transfer from semi-solid macromolecules. However, at lower field strengths including 1.5T the peak B1 field (1~25Hz) is on the same order as the R2 of myocardium. These effects should be kept in mind when considering field strength for cardiac CEST imaging. Finally, a sensitivity limit exists to the detection of creatine CEST contrast due to the presence of nuclear Overhauser effects at -1.8ppm. As such, negative

MTR_{asym} values at 1.8ppm reflect creatine contrast that is below this threshold. Future methodological development, or alternative methods including chemical exchange rotation transfer may eliminate the presence of negative values.

As mortality rates from cardiovascular disease continue to be driven by increased non-ischemic etiologies, the ability to quantify changes in cardiomyocyte metabolism may prove increasingly useful. In this study we demonstrated the ability to phenotype changes in creatine CEST contrast in the hearts of obese adults and revealed a correlation between reduced creatine levels and elevations in visceral fat mass and certain measures of LV mass. With further application to the study of the obese heart, it may be possible to distinguish between the impacts of fat mass distribution, hemodynamic forces, and body mass on cardiomyocyte metabolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Units and abbreviations

CEST	Chemical exchange saturation transfer
MRI	Magnetic resonance imaging
LV	Left ventricle
CK	Creatine kinase
ATP	Adenosine tri-phosphate
PCr	Phospho-creatine
MRS	Magnetic resonance spectroscopy
BMI	Body mass index
DXA	dual-energy X-ray absorptiometry
FOV	Field of view
ppm	Part per million
BSA	Body surface area
WASSR	Water saturation shift referencing

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Figure 1.

Longitudinal strains are preserved in obese adults. (a) Representative global longitudinal strain waveforms from obese and healthy adults. (b) Peak longitudinal strain, (c) longitudinal systolic strain rate (dGLS/dt_systolic) and (d) longitudinal diastolic strain rate (dGLS/dt_diastolic) were preserved in obese adults.

Figure 2.

Circumferential strain is preserved in obese adults. **(a)** Representative end diastolic (ED) and end systolic (ES) tagged images and **(b)** corresponding circumferential strain (Ecc) waveforms from healthy (left) and obese (right) adults are shown. Both **(c)** peak Ecc and systolic strain rate (dEcc/dt_systolic) were preserved in obese adults.

Figure 3. Representative CEST-weighted images. (a,d) Reference scans acquired without CEST preparation. Images acquired following CEST-preparation at offsets of 1.8ppm (b,e) and 0ppm (c,f) relative to water resonance show reduced signal intensity compared to the reference scans. Saturation of the septum at 0ppm was uniform in all patients, but both B0 and B1 inhomogeneity lead to inconsistent CEST-weighting in the free wall.

Figure 4.

CEST-MRI reveals reduced creatine in obese myocardium. **(a)** Representative Z-spectra display the mean septal signal intensity at each offset image normalized to a reference image. **(b)** Corresponding MTR_{asymp} waveforms reveal reduced creatine CEST contrast at 1.8ppm (dashed line) in the obese adult. **(c)** Creatine contrast was consistent among healthy adults, but significantly reduced and more heterogeneous among obese adults.

Figure 5.

Myocardial creatine contrast is inversely correlated with **(a)** total body fat ($\rho = -0.449$, $p = 0.011$), **(b)** visceral fat mass ($\rho = -0.582$, $p = 0.001$) and **(c)** septal wall thickness ($\rho = -0.441$, $p = 0.013$) correlation error bands are confidence intervals of 95%.

Figure 6.

No correlation was observed between creatine CEST contrast and **(a)** peak circumferential shortening, **(b)** global longitudinal shortening, or **(c)** global longitudinal diastolic strain rate (values are found in Table 3) correlation error bands are confidence intervals of 95%.

Table 1.**Participant Demographics**

	Healthy (n=11)	Obese (n=20)
Age	28.6 ± 3.0	32.7 ± 5.2
Gender		
Female	7	11
Male	4	9
Race		
White	10	17
African American	0	2
Hispanic	0	1
Asian	1	0
Weight (kg)	64.5 ± 8.1	110.1 ± 21.9
BMI (kg/m ²)	22.3 ± 1.2	37.3 ± 5.2
Body Surface Area (m ²)	1.7 ± 0.1	2.3 ± 0.3
Total Body Fat (%)	24.8 ± 4.7	44.5 ± 6.6

Data are presented as mean ± SD.

Table 2.

Cardiac structural and functional measures

	Healthy	Obese	P-value
End diastolic volume (ml)	148.4 ± 28.3	169.2 ± 51.8	0.17
End diastolic volume index (ml/m ²)	84.9 ± 13.7	73.1 ± 15.9	0.049
End systolic volume (ml)	44.9 ± 9.8	52.3 ± 26.4	0.28
End systolic volume index (ml/m ²)	25.8 ± 5.7	22.4 ± 9.5	0.24
Stroke volume (ml)	103.5 ± 22.2	116.9 ± 37.0	0.23
Stroke volume index (ml/m ²)	59.1 ± 10.5	50.7 ± 12.7	0.067
Ejection fraction (%)	69.6 ± 4.3	69.4 ± 9.3	0.95
Left ventricular mass (g)	112.5 ± 37	144.3 ± 47	0.057
Left ventricular mass index (g/m ²)	64 ± 16	62 ± 16	0.85
Septal wall thickness (cm)	0.84 ± 0.13	0.94 ± 0.17	0.073
Mass:volume ratio (g/ml)	0.75 ± 0.15	0.86 ± 0.16	0.093
Heart rate (beat/min)	65 ± 10	74 ± 10	0.042
Cardiac output (L/min)	6.9 ± 1.4	8.4 ± 2.1	0.031
Cardiac output index (L/min/m ²)	3.96 ± 0.86	3.65 ± 0.67	0.33

Data are presented as mean ± SD.

Table 3.

Correlation of Creatine CEST with Ventricular Structure and Function

	Pearson's (ρ)	P-value
Total body fat (%)	-0.448	0.011
Visceral fat (g)	-0.582	0.001
Body mass index (kg/m ²)	-0.658	0.001
End diastolic volume index (ml/m ²)	-0.024	0.90
End systolic volume index (ml/m ²)	0.121	0.52
Stroke volume index (ml/m ²)	-0.050	0.79
Left ventricular mass index (g/m ²)	-0.147	0.43
Septal wall thickness (cm)	-0.441	0.013
Ejection fraction (%)	-0.214	0.25
Cardiac output (L/min)	-0.543	0.002
Cardiac output index (L/min/m ²)	-0.179	0.33
Global circumferential strain (%)	0.030	0.87
Septal circumferential strain (%)	-0.063	0.74
Systolic circumferential strain rate (%/s)	0.134	0.47
Septal systolic circumferential strain rate (%/s)	0.232	0.21
Global longitudinal strain (%)	0.109	0.56
Systolic longitudinal strain rate (%/s)	-0.158	0.40
Diastolic longitudinal strain rate (%/s)	-0.121	0.52

Pearson's correlations were used to evaluate whether creatine CEST contrast correlates with other measured parameters.