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Massachusetts Institute of Technology

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Mapping the Unseen: In Vivo CEST-MRI of Creatine Reveals Improved Cardiac Energetics in Subjects with Obesity Following Bariatric Surgery

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Mapping the unseen: *in vivo* CEST-MRI of creatine reveals improved cardiac energetics in subjects with obesity following bariatric surgery

Salva R. Yurista MD PhD[1,2,5,6], Shi Chen BS[1,2,5,6], Robert A. Eder BA[1,2], Thomas Garrett BS[1,2,5,6], W. Scott Butsch MD[4], Ali Aminian MD[4], W.H. Wilson Tang MD[5], Christian T. Farrar PhD[2], Denise Gee MD[9], E. Dale Abel MD PhD,[10] Saumya Das MD PhD[1], Christopher T. Nguyen PhD*[1,2,3,5,6,7,8]

[1]Cardiovascular Research Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, 02124, USA
[2]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, 02129, USA
[3]Division of Health Science Technology, Harvard-Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
[4]Bariatric and Metabolic Institute, Cleveland Clinic, Cleveland, OH, 44195, USA
[5]Department of Cardiovascular Medicine, Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, OH, 44195, USA
[6]Cardiovascular Innovation Research Center, Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, OH, 44195, USA
[7]Imaging Institute, Cleveland Clinic, Cleveland, OH, 44195, USA
[8]Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, 44106,USA
[9]MGH Weight Center, Department of Surgery, Massachusetts General Hospital, Boston, MA, 02114, USA.
[10]Department of Medicine, David Geffen School of Medicine and UCLA Health, Los Angeles, CA, 90095, United States

***Corresponding author:**

Christopher T. Nguyen, PhD
Cardiovascular Innovation Research Center
Heart, Vascular, and Thoracic Institute
Cleveland Clinic
9500 Euclid Ave, JJ50 S
Cleveland, OH 44195
Phone: 216-219-7053 / Email: nguyenc6@ccf.org

Key points:

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- *This study examines the impact of bariatric surgery on cardiac function and metabolism.*
- *Subjects with obesity has lower cardiac creatine levels.*
- *Bariatric surgery reduces weight, BMI, LV mass index, and epicardial fat.*
- *These changes are accompanied improvement in LVEF and cardiac energetics.*

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Introduction

The heart is constantly consuming energy throughout its lifetime, with energetic reserve capacity to respond to increased demand. Cardiac metabolic derangements has previously been reported in several clinical contexts including myocardial infarction, heart failure, and obesity.[1,2] While cardiac ATP at rest is often maintained in obesity, previous study showed impaired cardiac energy reserve via creatine kinase reaction and it may be involved in the progression to heart failure.[1,2] Efforts to study cardiac energy substrate metabolism *in vivo* has been a field of active research for more than a century. Among others, chemical exchange saturation transfer (CEST) is a promising metabolic imaging technique which can be used for creatine mapping in the heart.[3] This prospective study examined the impact of bariatric surgery on cardiac function and metabolism.

Methods

Subjects with moderate to severe obesity (body mass index, BMI ≥ 35 kg/m^2) who underwent gastric sleeve surgery and subjects with normal BMI (n=10) were consented and recruited with approval from the Institutional Review Board of the Massachusetts General Hospital and conformed the Declaration of Helsinki. Cardiac magnetic resonance imaging (CMR) was performed before and after surgery on a 3T MRI Skyra clinical scanner (Siemens Medical, Germany). The imaging protocol included conventional CINE, fat-water imaging, native T1/T2 relaxometry, and CEST-CMR for myocardial creatine mapping. In addition, a phantom doped with varying

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creatine concentrations was built and scanned to validate the relationship between asymmetric magnetization transfer ratio (MTR_{asym}) and creatine concentration. Creatine CEST-CMR scans were performed using a previously published CEST preparation pulse train[3] coupled with a reduced field of view echo planar imaging readout to reduce MT effects and was gated with ECG and respiratory navigation. The segmentation of CINE images was performed on Segment software (Medviso, Sweden), while segmentation of visceral fat, native T1, and T2 was performed with Osirix (Pixmeo, Switzerland). Post-processing of CEST images was performed with custom-written software in Python. Data are presented as mean ± standard errors of the means. The results were compared using paired t-test. One-way ANOVA followed by Bonferroni test was used to compare differences of means among more than two groups. *p*-value *<0.05* was considered significant.

Results

Six subjects [mean BMI 40.5 ± 2.6 kg/m²] had completed the second CMR (i.e. post-surgery), with a median follow-up of 10 months. The median age was 46.5 years, 67% were female, and 16.67% had type 2 diabetes. Bariatric surgery induced significant reduction in body weight (*Fig.A*) with achieved mean BMI of 31.0 ± 2.0 kg/m² (*Fig.B)*. In addition, bariatric surgery was also associated with significant reduction in left ventricular (LV) mass, LV mass index (i.e. LV mass Indexed to body surface area), and epicardial adipose tissue (EAT) volume (*Fig.C-E*). This was accompanied by an improvement in LV ejection fraction compared to baseline value (*Fig.F*). No

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significant changes were found in end-diastolic and systolic volume (129 ± 12 to 127 ± 7 ml and 58 ± 2 to 49 ± 4 ml, respectively), global longitudinal strain (17.9±1.5% vs. 17.7±0.9%), as well as myocardial native T1 and T2 values (*Fig.G-H*). Representative MRI images of Dixon-based water and fat content, CINE, and native T1 and T2 maps, respectively, are depicted in *Fig.I-K*. Phantom experiment revealed creatine concentration dependent MTR_{asym}(*Fig.L*). A significant increase in creatine CEST contrast was observed following bariatric surgery (*Fig.M-N)*. Compared to normal-weight subjects (*n=10*), CEST contrast was significantly lower in subjects with obesity; and it was normalized after the surgery and statistically similar to those with normal BMI, suggesting an improvement in myocardial energetics(*Fig. O*).

Discussion

In line with previous studies,[4,5] our study demonstrates that bariatric surgery in addition to reducing body weight and BMI, could significantly reduce LV mass and EAT. However, our study also provides some new information, specifically the observation of an improvement in LV ejection fraction and myocardial creatine content detected by CEST-CMR following bariatric surgery. Although the mechanism of actions underlying LV mass regression and EAT reduction is unclear, weight loss in obesity is known to improve LV geometry and possible candidate pathways include neurohormonal pathways that might also improve CV outcomes. Furthermore, it may be speculated that, at least in part, LVEF improvement after surgery resulted from the reduction in EAT.

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In concordance with our findings for myocardial energetics, a previous study reported metabolic derangement in cardiac energetics in obesity[2], specifically, the myocardial creatine signal measured by CEST-CMR, was lower in subjects with obesity compared to subjects with normal BMI.[2] A strong correlation between increased body and visceral fat volumes and reduced myocardial energetics was also observed.[2] Our findings extend this observation as we demonstrate improved cardiac structure and function as well as normalization of cardiac energetics after bariatric surgery. This study also highlights that bariatric surgery reverses the energetic changes and might be a potential modifiable pathway to prevent the progression to heart failure. Future studies should include a larger sample size with a separate appropriate control group. Furthermore, incorporating direct measurements of phosphocreatine/ATP using ^{31}P-MRS and cardiac arterio-venous gradients into future studies would enable a more comprehensive assessment of cardiac metabolism and provide additional insights into the reliability of creatine mapping using CEST-MRI, as well as its correlation with cardiac energetics.

Conclusion

These results demonstrate that in addition to reducing BMI, bariatric surgery may favorably affect cardiac function and metabolism. An important aspect is the ability to measure myocardial energetics in vivo using conventional proton-based MRI scanners without invasive biopsy or ionizing

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radiation. This allows for repeated measurements in longitudinal studies and the potential for in vivo metabolic imaging to become a valuable clinical tool.

Key words: obesity, bariatric surgery, myocardial energetics, cardiac function, chemical saturation exchange transfer, magnetic resonance imaging.

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Conflict of interest

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Statement of Informed Consent

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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Figure legend

The impact of bariatric surgery on cardiac function and metabolism. Changes in body weight **(A)**, body mass index **(B)**, LV mass **(C)**, LV mass index **(D)**, epicardial fat **(E)**, LV ejection fraction **(F)**, T1 value **(G)** and T2 value **(H)** after bariatric surgery. **(I-K)** Representative images of fat-water content, cine CMR, and T1 and T2 maps, respectively. **(L)** Graphs shows creatine signal (MTR_{asym}) for each concentration obtained from CEST-CMR phantom experiment. **(M)** Representative masked images of cardiac CEST-CMR at 1.8 ppm. **(N)** Myocardial creatine content before and after bariatric surgery. **(O)** Comparison of CEST contrast between subjects with normal BMI and subjects with obesity. LV indicates left ventricle; CMR indicates cardiac magnetic resonance imaging. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

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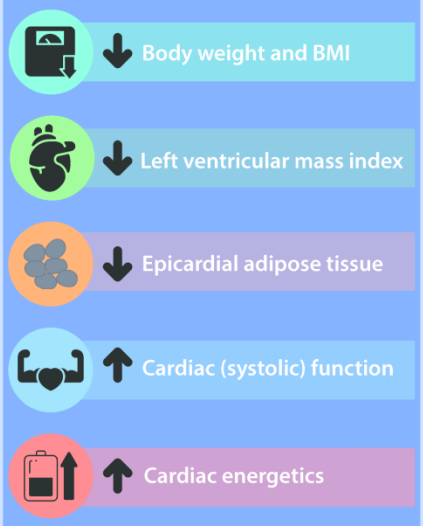
METHODS

- Subjects with moderate to severe obesity who underwent gastric sleeve surgery and normal BMI were recruited and consented.
- Cardiac MRI was performed before and after surgery using a 3T MRI.
- The imaging protocol included conventional CINE, fat-water imaging, native T1/T2 relaxometry, and CEST-CMR for myocardial creatine mapping.

RESULTS



CONCLUSION

- Bariatric surgery may improve cardiac function and metabolism beyond BMI reduction.
- Conventional proton-based MRI can quantify myocardial energetics in vivo, without invasize biopsy or ionizing radiation.
- This allows for repeatable longitudinal studies and potential for metabolic imaging as a clinical tool.

Salva Yurista, Shi Chen, Robert Eder, Thomas Garrett, W. Scott Butsch, Ali Aminian, W.H. Wilson Tang, Christian T. Farrar, Denise Gee, E. Dale Abel, Saumya Das, Christopher T. Nguyen

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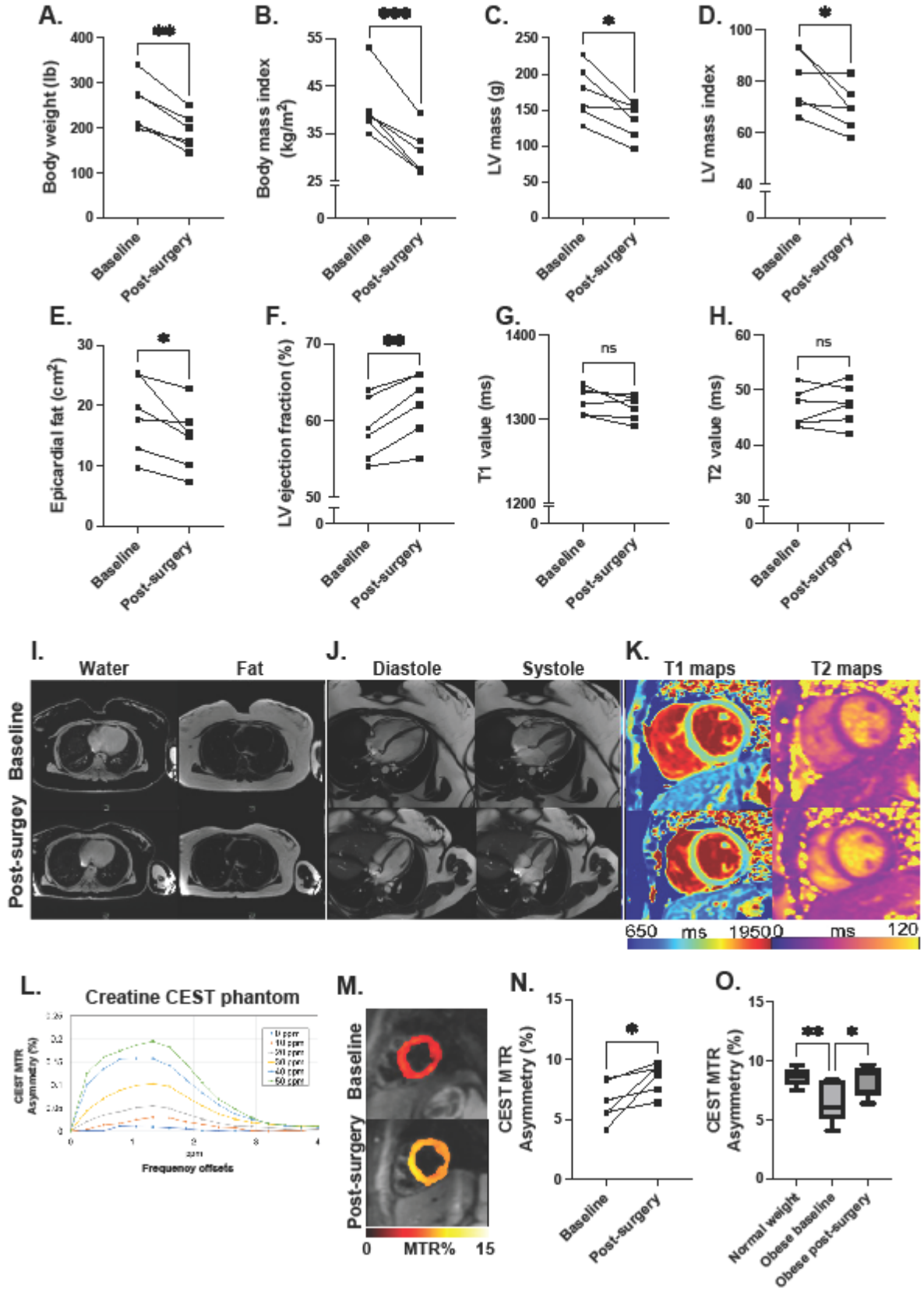
A.
Body weight (lb)
B.
Body mass index (kg/m²)
C.
LV mass (g)
D.
LV mass index
E.
Epicardial fat (cm²)
F.
LV ejection fraction (%)
G.
T1 value (ms)
ns
H.
T2 value (ms)
ns
Baseline
Post-surgery
I.
Water
Fat
J.
Diastole
Systole
K.
T1 maps
T2 maps
650 ms 1950
0 ms 120
L.
Creatine CEST phantom
CEST MTR Asymmetry (%)
Frequency offsets
M.
Baseline
Post-surgery
0 MTR% 15
N.
CEST MTR Asymmetry (%)
O.
CEST MTR Asymmetry (%)
Normal weight
Obese baseline
Obese post-surgery