

1 **Myocardial Tissue Phase Mapping Reveals Impaired Myocardial Tissue Velocities in Obesity**

2 ¹Oliver J Rider, Ezimamaka Ajufo¹, ¹Mohammed K Ali, Steffen E Petersen², ¹Richard Nethononda

3 ¹Jane M Francis, ¹Stefan Neubauer

4 ¹*Oxford Centre for Clinical Magnetic Resonance Research, University of Oxford, UK*

5 ² *William Harvey Research Institute, Queen Mary, University of London, UK*

6

7 From the Division of Cardiovascular Medicine and University of Oxford Centre for Clinical Magnetic Resonance

8 Research, Radcliffe Department of Medicine University of Oxford, Oxford, UK

9 *Correspondence to:*

10 Dr Oliver Rider BA BMBCCh MRCP DPhil

11 Clinical Lecturer Cardiovascular Medicine

12 Division of Cardiovascular Medicine,

13 John Radcliffe Hospital,

14 Oxford, OX3 9DU, UK

15 (Tel) ++441865221867

16 (Fax) ++441865222077

17 Email oliver.rider@gmail.com

18

19 **Funding:** The study was supported by a grant from the Wellcome Trust and the Oxford NIHR

20 Biomedical Research Centres funding scheme.

21 **Word Count:** 3,426

22 **Disclosures:** None

23 **Running Title:** Obesity and Myocardial Tissue Phase Mapping

24

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23

Abstract

Purpose: Although obesity is linked to heart failure on a population level, not all obese subjects develop cardiac failure. As a result, identifying obese subjects with subclinical changes in myocardial velocities may enable earlier detection of those susceptible to developing overt heart failure. As echocardiography is limited in obesity due to limited acoustic window, we used phase contrast magnetic resonance imaging to assess myocardial velocities in obese and normal weight subjects.

Methods: Normal weight (BMI 23±3; n=40) and obese subjects (BMI 37±7; n=59) without identifiable cardiovascular risk factors underwent MRI (1.5 Tesla) to determine left ventricular myocardial velocities using phase contrast tissue phase mapping.

Results: Systolic function was not different between normal and obese subjects (LVEF 67±5 vs 68±4, p=0.22). However, obesity was associated with significantly impaired peak radial and longitudinal diastolic myocardial velocity (by 13% and 19% respectively, both p <0.001). In addition time-to-peak longitudinal diastolic velocity was delayed in obesity (by 39ms, p <0.001). In addition, peak longitudinal diastolic strain was 20% lower in obesity (p =0.015) and time-to-peak longitudinal diastolic strain rate significantly delayed in obesity (by 92ms, p <0.001). Although peak radial systolic velocity was similar between obese and normal weight subjects (p = 0.14) peak longitudinal systolic velocity was 7% lower in the obese cohort (p = 0.02).

Conclusion: In obesity without co-morbidities, tissue phase mapping has shown subclinical changes in systolic and diastolic function. Given the link between obesity and heart failure, early detection of changes may become clinically important to prevent disease progression.

1 **Introduction**

2 Obesity is associated with an increased cardiovascular mortality rate, and even greater risk is associated
3 when the BMI exceeds 35 kg/m². [1] In addition, there is a spectrum of functional cardiac changes that
4 occur in obesity ranging from subclinical diastolic dysfunction to overt systolic failure. [2,3] Although
5 there is a clear relationship between obesity and heart failure on a population level, [4] the majority of
6 smaller cohort studies report that obesity itself has little or no effect on global measures of systolic
7 function such as LV ejection fraction [5]. This suggests that, although some individuals are susceptible
8 to developing obesity cardiomyopathy and heart failure, it is not a universal phenomenon. Whilst
9 obesity related subclinical impairment of LV systolic and diastolic function [6] may precede the
10 development of overt systolic failure, there are no long term prospective studies to demonstrate this.
11 However, it is now generally accepted that a longer duration of obesity is likely to be linked to the
12 development of manifest LV systolic dysfunction. [7] As a result, detecting early changes in systolic
13 function is likely to be important in identifying those at risk of developing heart failure.

14 In addition to changes in systole, obesity, both with and without additional co-morbidities, has also been
15 linked to diastolic dysfunction using a wide range of non-invasive imaging modalities. [8-10] As even
16 asymptomatic diastolic dysfunction has now been proved to be associated with the development of heart
17 failure [11,12], detecting this is again clinically important, and potentially identifies those at risk of
18 developing clinically manifest heart failure and allowing early intervention in the form of weight loss
19 therapies.

20 Despite this, current imaging techniques to detect early, subclinical myocardial dysfunction in obesity
21 rely almost exclusively on echocardiography, which is severely limited in obesity due to acoustic
22 window constraints imposed by excess chest wall fat. In addition, 2D echocardiography measures of
23 systolic and diastolic dysfunction lack sensitivity and there is now emerging evidence that regional
24 measures of both longitudinal and radial function have additional value. [13] Cardiovascular magnetic
25 resonance imaging (CMR) derived Tissue Phase Mapping (TPM) overcomes these limitations by not

1 only being able to provide accurate, regional, 3-dimensional measures of systolic and diastolic function
2 but also being able to do so irrespective of the amount of chest wall fat. [14-17] As a result, we aimed to
3 use TPM to quantify regional 3D cardiac tissue motion in 59 obese subjects with no cardiovascular risk
4 factors and compared them to 40 normal weight controls. [18]

6 **Methods**

7 *Ethics and Study Cohort*

8 This study was a prospective study of ninety-nine healthy subjects (59 obese, 22 male, BMI > 30kg/m²
9 and 40 normal weight controls, 18 male, BMI 18.5-24.9 kg/m², Table 1). The study was approved by the
10 local ethics committee and therefore has been performed in accordance with the ethical standards laid
11 down in the 1964 Declaration of Helsinki and its later amendments. Informed written consent was
12 obtained from each subject.

13 All subjects were screened for identifiable cardiac risk factors and obesity-related co-morbidities.
14 Subjects were excluded if they had a history of; any cardiovascular disease, chest pain, tobacco
15 smoking, hypertension, peripheral vascular disease, contraindications to MR imaging, diabetes (fasting
16 glucose level 7.1 mmol), a fasting total cholesterol level ≥ 6.5 mmol/l, use of any prescription
17 medications or a history compatible with obstructive sleep apnoea. All subjects had a normal 12 lead
18 electrocardiogram, normal cardiovascular examination, normal global and regional resting cardiac
19 function on MR imaging, and did not perform more than three sessions (defined as 30 minutes) of
20 sweat-producing exercise per week.

21 *Blood tests*

22 Fasting blood tests for glucose and cholesterol were taken on the day of the scanning and analysed as
23 described [10].

1 ***Bio-Impedance analysis***

2 Bio-electrical impedance was used to determine total body fat mass, and lean body mass using Bodystat
3 ©1500 analyser. The use of bioimpedance analysis has become routine in clinical research investigating
4 body composition analysis. Although not the gold standard for analysis of body composition, it has been
5 shown to have close correlation with DEXA assessments in multiple studies [19].

7 ***Magnetic Resonance Imaging of the Left Ventricle***

8 All imaging was prospectively cardiac gated with a precordial three lead ECG and acquired during end
9 expiration breathhold. Images were acquired using a steady state free precession (SSFP) sequence with an
10 echo time (TE) of 1.5ms, a repetition time (TR) of 3.0ms, temporal resolution 47.84ms and a flip angle
11 of 60° as previously described .[20] SSFP cine sequences were used to acquire localisation images
12 followed by a SSFP right and left ventricular short axis stack of contiguous images (slice thickness
13 7mm, interslice gap 3mm).

15 ***Tissue Phase Mapping***

16 All TPM imaging was performed at 1.5-T (Sonata; Siemens Medical Solutions, Erlangen, Germany).
17 Steady-state free precession cine images (repetition time ms/echo time ms, 3.0/1.5; flip angle, 60°;
18 section thickness, 7 mm; intersection gap, 3 mm; temporal resolution, 45 ms) were acquired in
19 horizontal and vertical long-axis views, and short-axis. These were followed by three single breath hold
20 phase-contrast (TPM) images at the base, mid-ventricle and apex of the LV. TPM was performed using
21 a prospectively triggered black blood segmented k-space gradient-echo sequence (6.2/4.5; flip angle,
22 15°) with first-order flow compensation in all dimensions to minimize artefacts from flow or motion as
23 previously described [21] (field of view 255 × 340-mm, slice thickness 8mm, temporal resolution 37–87
24 ms, 17–29 heartbeats (adjustable to breath-holding capability)).

1 For segmental analysis the LV was divided according to the AHA 16-segment model (6 basal, 6
2 midventricular, and 4 apical regions, Figure 1 & 2). For each segment, peak and time-to-peak radial and
3 long-axis velocities in systole and diastole were calculated and averaged for each group. Results are
4 presented as bulls eye plots permitting a direct comparison between obese and normal weight controls.
5 Global average velocities combined across all segments were calculated, in addition, epicardial and
6 endocardial values were calculated (separated by the outer and inner 50% of the myocardium
7 respectively).

8 9 *Data Analysis*

10 **Left Ventricular Morphology**

11 Image analysis for ventricular volumes and mass was performed using cmr42 © imaging analysis
12 software (Circle Cardiovascular Imaging Inc, Calgary, Canada). The short axis stack was analysed
13 manually, contouring the endocardial borders from base to apex at end-diastole and end-systole. The
14 epicardial border was contoured at end-diastole to yield myocardial mass. Ventricular mass (g) was
15 calculated as the epicardial volume minus the endocardial volume multiplied by 1.05 (specific gravity of
16 myocardium).

17 18 **Tissue Phase Mapping**

19 TPM data was analysed using in house software in Matlab Version 2012a (Mathworks, Natick,
20 Massachusetts, USA) as previously described.[21] In brief, manual endocardial and epicardial contour
21 segmentation was performed. Radial and circumferential velocity values were then calculated from in-
22 plane velocities for each pixel on the basis of an internal polar coordinate system positioned at the centre
23 of the left ventricle (Figure 1). The longitudinal velocity values were encoded in the acquisition and
24 were used without correction. The mean velocity was computed for pixels within the epicardial (inner
25 half of the wall thickness), endocardial (outer half of the wall thickness), and transmural regions.

1

2 *Statistical Analysis*

3 All statistics were analysed using commercial software packages (SPSS 20; SPSS, Chicago, Ill, STATA,
4 StataCorp, Texas). All data were subjected to Kolmogorov–Smirnov tests to establish normal
5 distribution of the data. All normally distributed results are presented as the mean \pm standard deviation;
6 Normally distributed data was analysed using independent t-test or ANOVA analysis where appropriate,
7 with Bonferroni correction. Values of $p < 0.05$ were considered as statistically significant.

8

9 **Results**

10 *Anthropomorphic Data*

11 As expected, weight and body mass index were higher in the obese cohort. Both groups were well
12 matched for age, systolic blood pressure, diastolic blood pressure, fasting cholesterol and fasting
13 glucose concentration, with no statistically significant difference in mean values between the two groups
14 (Table 1).

15

16 Left Ventricular Characteristics

17 As expected, obesity was associated with significantly elevated LV mass (by 20%, $p < 0.01$, Table 1) and
18 higher stroke volume (by 12%, $p = 0.03$). Of note LV end-diastolic volume, and LVEF were similar
19 between normal weight and obese subjects (Table 1).

20

21 Tissue Phase Mapping

22 **Systolic Velocity**

23 *Radial Systolic Velocity* When comparing transmural measurements, there was no significant difference
24 in either peak radial systolic velocity (obese 2.9 ± 1.3 vs normal 3.1 ± 1.1 cm/s, $p = 0.14$) or time-to-

1 peak radial systolic velocity (obese 178 ± 84 vs normal 175 ± 82 ms, $p = 0.51$) when comparing obese
2 and normal weight cohorts (Figure 2). Peak endocardial and epicardial radial systolic velocities and
3 time-to-peak endocardial radial systolic velocities were also similar between obese and normal weight
4 groups (all $p > 0.25$, Figure 3)

5 ***Longitudinal Systolic Velocity*** In contrast to the radial systolic velocities, peak longitudinal systolic
6 velocity was 7% lower in the obese cohort (obese 4.4 ± 3.0 vs normal 4.7 ± 3.0 cm/s, $p = 0.02$, Figure
7 2). However, time-to-peak longitudinal systolic velocity was similar between cohorts (obese 195 ± 145
8 vs normal 204 ± 165 ms, $p = 0.28$). Interestingly, although epicardial velocities followed the same
9 pattern with a 11% reduced peak longitudinal systolic velocity ($p < 0.001$) and a similar time-to-peak
10 longitudinal systolic velocity ($p > 0.30$) endocardial time-to-peak longitudinal systolic velocity was
11 delayed in obesity (by 10ms, $p < 0.001$, Figure 3).

12 Overall this suggests that obesity, without risk factors, does not impair radial systolic function but is
13 associated with reduced longitudinal systolic function.

14 **Diastolic Velocity**

15 ***Radial Diastolic Velocity*** When comparing all segments, peak radial diastolic velocity was 13% lower
16 in the obese cohort (obese 3.5 ± 1.5 vs normal 4.0 ± 1.6 cm/s, $p < 0.001$, Figure 2)). However, time-to-
17 peak radial diastolic velocity was similar between cohorts (obese 496 ± 89 vs normal 496 ± 67 ms, $p =$
18 0.90). This pattern was repeated with both endocardial and epicardial peak radial diastolic velocities
19 (epicardial; 7% lower, endocardial; 13% lower in obesity, both $p < 0.001$) and time-to-peak radial
20 diastolic velocities (similar between obese and normal weight groups all $p > 0.28$, Figure 3).

21 ***Longitudinal Diastolic Velocity*** In agreement with the radial diastolic velocities, transmural peak
22 longitudinal diastolic velocity was 19% lower in the obese cohort (obese 6.1 ± 3.4 vs normal 7.5 ± 3.5
23 cm/s, $p < 0.001$, Figure 2). Furthermore, time-to-peak longitudinal diastolic velocity was 39ms delayed

1 (obese 507 ± 84 vs normal 468 ± 11 ms, $p < 0.001$). This pattern was repeated with endocardial and
2 epicardial analysis, both peak longitudinal diastolic velocities were reduced (both $p < 0.001$) and time-to-
3 peak longitudinal diastolic velocities delayed (both by 38ms, $p < 0.001$, Figure 3).

4 As both radial and longitudinal diastolic velocities are impaired in obesity (where only longitudinal
5 systolic function was affected by obesity) this suggests that diastolic function is more susceptible to the
6 effects of obesity than systolic function.

7 **Rotational Velocities**

8 **Basal Rotational Velocities** There was no significant difference in peak basal systolic clockwise
9 rotational velocity (twist) between the obese and normal weight cohorts (obese 2.3 ± 1.2 vs normal $2.2 \pm$
10 0.8 cm/s, $p = 0.08$). In contrast, peak diastolic counter-clockwise rotation (untwist) was significantly
11 lower in the obese cohort (by 17%, obese 2.1 ± 1.3 vs normal 2.5 ± 1.2 cm/s, $p < 0.001$). In addition,
12 time-to-peak diastolic untwisting velocity was significantly delayed in obesity (by 53%, obese $307 \pm$
13 205 vs normal 200 ± 214 ms, $p < 0.001$).

14 **Apical Rotational Velocities** In contrast to the basal rotational velocities, obesity was associated with a
15 significantly higher peak apical systolic counter-clockwise rotational velocity (obese 2.6 ± 1.3 vs normal
16 2.3 ± 1.4 cm/s, $p = 0.03$). In agreement with other velocity measures, peak diastolic counter-clockwise
17 rotation (untwist) was significantly lower in the obese cohort (obese 1.8 ± 1.0 vs normal 2.2 ± 0.9 cm/s,
18 $p = 0.03$). In addition, time-to-peak diastolic untwisting velocity was significantly delayed in obesity (by
19 53%, obese 307 ± 205 vs normal 200 ± 214 ms, $p < 0.001$).

20 **Left Ventricular Torsion and Strain Rate**

21 When comparing the obese and normal weight cohorts, there was no significant difference in either peak
22 systolic torsion rate (obese 18.0 ± 6.4 vs normal 16.3 ± 4.9 deg.s⁻¹.cm⁻¹ $p = 0.10$) or time-to-peak systolic
23 radial strain rate (obese 46 ± 12 vs normal 52 ± 19 ms, $p = 0.07$). In contrast, although peak diastolic

1 torsion rate was similar between cohorts (obese -15.1 ± 6.4 vs normal -14.8 ± 4.9 deg.s⁻¹.cm⁻¹ p =0.77),
2 time-to-peak diastolic radial torsion was significantly delayed in obesity (obese 103 ± 45 vs normal $48 \pm$
3 53 ms, p <0.001).

4 In comparison to this, although both peak longitudinal systolic strain rate (obese -1.1 ± 0.5 vs normal -
5 1.1 ± 0.3 s⁻¹, p =0.78) and time-to-peak longitudinal systolic strain rate (obese 58 ± 22 vs normal $50 \pm$
6 21 ms, p =0.07) were similar between cohorts, peak longitudinal diastolic strain was significantly lower
7 in obesity (obese -1.2 ± 0.5 vs normal -1.5 ± 0.6 s⁻¹, p =0.015) and time-to-peak longitudinal diastolic
8 strain rate significantly longer in obesity (obese 136 ± 44 vs normal 64 ± 56 ms, p <0.001).

9 Overall this would suggest that obesity is associated with impaired diastole with longer time to peak
10 torsion rate and both lower longitudinal diastolic strain rate and longer time-to-peak longitudinal
11 diastolic strain rates.

12 13 **Discussion**

14 Subclinical changes in systolic and diastolic function have both been widely reported in obesity.
15
16 However, many studies have used global echocardiography measures of function which are limited in
17 obesity, mainly due to acoustic window constraints. This study has utilized the inherent advantages of
18 CMR to record regional, 3 dimensional tissue velocities using tissue phase mapping imaging. We have
19 shown that obesity, even in the absence of cardiovascular risk factors, is associated with both reduced
20 peak longitudinal systolic velocities and reduced peak radial and longitudinal diastolic velocities. In
21 addition we have also shown that longitudinal diastolic strain is impaired in obesity.

22 **Systolic Function in Obesity**

23 Although there is a clear relationship between obesity and heart failure on a population level, [4] the
24 majority of smaller cohort studies report that obesity has little or no effect on global measures of systolic
25 function such as LV ejection fraction [5]. We have showed this again in this study with left ventricular

1 ejection fraction being similar between the obese and normal weight groups. This study has shown
2 however that whilst global left ventricular ejection fraction remains unchanged, obesity is associated
3 with reduced longitudinal systolic velocities, highlighting that subclinical changes in systole are present
4 in this obese group. Identifying this is of great importance as these subtle changes in systole may
5 precede the development of overt systolic failure and help identify those who are at risk of further
6 deterioration in systolic function, and development of heart failure.

7

8 **Diastolic Function in Obesity**

9 Obesity, both with and without additional co-morbidities, has also been linked to diastolic dysfunction
10 using a wide range of non-invasive imaging modalities. [8-10,22] Although traditionally ignored, this is
11 becoming clinically important as there is now emerging evidence that even asymptomatic diastolic
12 dysfunction is associated with the development of heart failure. [11,12] This study has not only shown
13 that peak diastolic myocardial velocities are reduced in both the radial and longitudinal direction but
14 also that peak longitudinal diastolic strain and time-to-peak longitudinal diastolic strain are impaired in
15 obesity. This highlights again that obesity without comorbidities is linked to diastolic dysfunction but, in
16 addition, that obesity affects both radial and longitudinal diastolic function. By studying regional, 3
17 dimensional imaging in both the radial and longitudinal direction, a more comprehensive assessment of
18 diastolic movement can be achieved, potentially allowing more subjects with subclinical dysfunction to
19 be identified.

20

21 **Pattern of Change Compared to Other Myocardial Disease Processes**

22 2D strain imaging has shown that evaluating deformation in the longitudinal, radial, and circumferential
23 directions is important to gain an understanding of the 3-dimensional geometry and myofibrillar
24 architecture of the LV, and is needed to accurately document LV systolic function. [23] As a result of
25 these studies, it has been shown that assessment of contraction of both the longitudinal and radial fibers

1 is important in determining LV systolic function .[24] Longitudinal LV diastolic and systolic function
2 were impaired before radial function in asymptomatic patients with cardiovascular risk factors and
3 preserved LV pump function [25] This pattern of early change in longitudinal function has also been
4 shown in diabetes [26]. It therefore appears that radial contractility compensates for reduced
5 longitudinal contractility in subclinical LV dysfunction, occurring in the absence of ischaemia or LV
6 hypertrophy, to maintain overall left ventricular ejection fraction. This pattern is again seen in this study
7 in the setting of obesity, without overt diabetes or cardiovascular risk factors. This suggests that in this
8 group it is an obesity specific factor that is driving these subclinical changes.

9

10 **Potential Mechanisms Behind Functional Changes in Obesity**

11 The mechanisms behind subclinical diastolic and systolic dysfunction in obesity are only partially
12 understood. [27] Myocardial contraction and relaxation are both determined by a combination of active
13 processes (including calcium homeostasis and myocardial energetics) [28] and passive processes related
14 to the physical properties of the left ventricle (intrinsic mechanical stiffness as determined by wall
15 thickness and chamber geometry). [29] It is likely that systolic and diastolic dysfunction in obesity is a
16 result of both passive and active mechanisms including LV hypertrophy and impairment in myocardial
17 energetics. [17,30-32] Using TPM, patients with left ventricular hypertrophy due to hypertensive heart
18 disease have previously been shown to have reduced systolic and diastolic velocities in both radial and
19 longitudinal directions, as well as reduced circumferential basal rotation. [33] It is therefore likely that
20 the reduction in myocardial velocities seen in this study is, at least in part, due to the elevated LV mass
21 that accompanies obesity. In addition, the association between reduced myocardial energetics and
22 diastolic dysfunction has been shown in multiple studies. [34,28] This is consistent with the concept that
23 an impairment in high-energy phosphate metabolism initially affects the ability of the sarcoplasmic

1 reticular Ca^{2+} ATPase (SERCA), the energetically most demanding of all enzymes involved in
2 contractile function, [35] to lower cytosolic Ca^{2+} and thus impairs diastolic function.

3 **Comparison to Other CMR Sequences**

4 Although the measurement of velocities in all three spatial directions is usually performed by phase-
5 contrast tissue phase mapping (as in this study), the main disadvantage of velocity encoding is the long
6 measurement time and sensitivity to background phase errors. In addition to TPM, there are now many
7 newer CMR sequences that can evaluate myocardial velocities including tagging and myocardial feature
8 tracking. The tagging technique enables measurement of displacement over time by mapping lines or a
9 grid on to the myocardium, performed either by spatial modulation techniques or by use of a delay
10 alternating with nutations for tailored excitation (DANTE) pulse train which is simultaneously applied
11 with a frequency encoding gradient.[36] The main disadvantages of tagging is the need of post-
12 processing to obtain the displacement of each point and the low spatial resolution resulting from the tag
13 spacing.[36] Although feature tracking enables the measurement of myocardial velocities from standard
14 SSFP cine images, larger measurement variability has brought recently made its application into the
15 clinical realm questionable. [37] Although this is the only study to date to use CMR to investigate
16 myocardial velocities in obesity, preliminary applications to patients with wall motion abnormalities
17 have promised considerable clinical potential for all of the CMR techniques.

18

19

20 **Conclusion**

21 Even in the absence of cardiovascular risk factors, obesity is associated with significant subclinical
22 changes in both systolic and diastolic function. Obesity *per se* is associated with reduced longitudinal
23 systolic function without change in radial systolic function. Obesity is also associated with multiple

1 markers of diastolic dysfunction including; impaired radial and longitudinal diastolic velocities, longer
2 time to peak torsion rate, lower longitudinal diastolic strain rate and longer time-to-peak longitudinal
3 diastolic strain rates. When compared to the single observed difference in longitudinal systolic velocity,
4 this larger number of differences in diastolic function would suggest that diastolic function is more
5 susceptible to the effects of obesity than systolic function. As magnetic resonance derived tissue phase
6 mapping is able to identify these changes in both the radial and longitudinal directions, irrespective of
7 body habitus, it has major advantages over ultrasound techniques. Given the link between obesity and
8 heart failure, early detection of changes in LV function using TPM is clinically important and may
9 prevent disease progression.

10

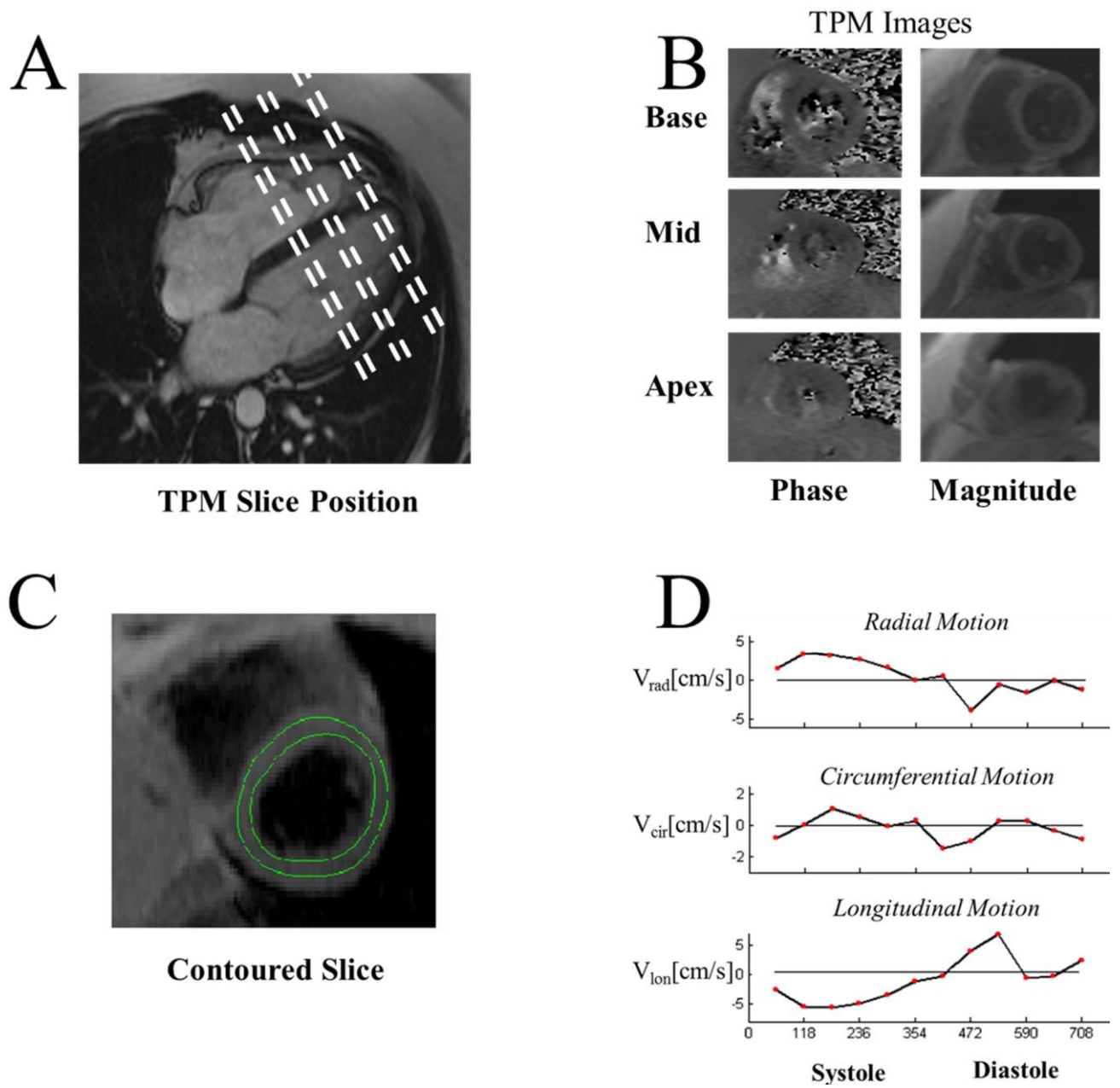


Figure 1. (A) Example slice positions relative to Horizontal Long Axis view, (B) TPM phase and magnitude images at the base, mid-ventricular and apical level, (C) Example of epicardial and endocardial contours on a basal slice and (D) An example of the generated radial, circumferential and longitudinal velocity graphs.

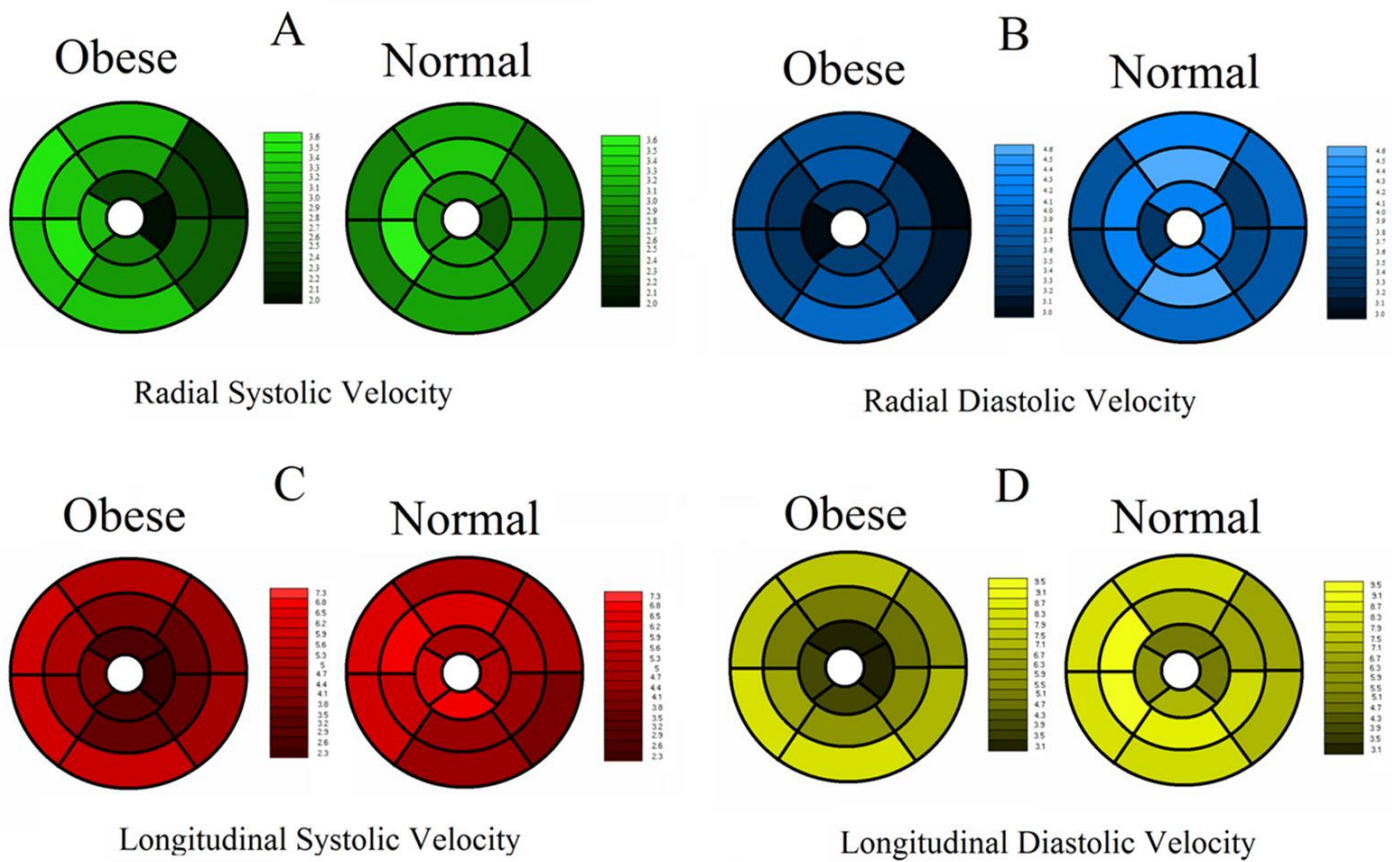


Figure 2. Transmural Systolic and Diastolic Velocities in Obesity and Normal Weight Plotted According to the 16 Segment AHA model. Colour scales represent myocardial velocity (cm/s). Darker areas denote myocardial lower velocities.

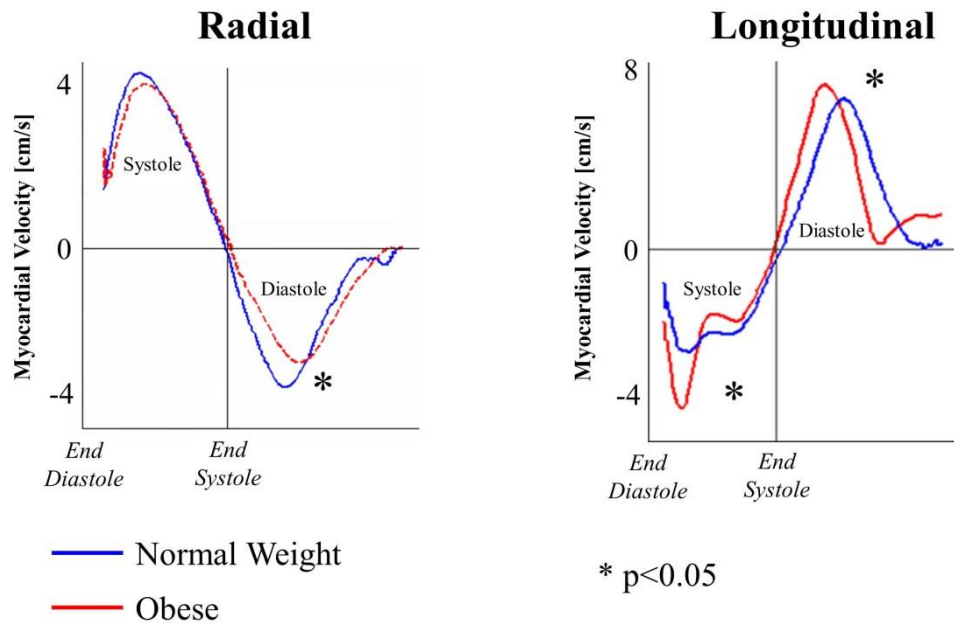


Figure 3. The Effect of Obesity on Global Myocardial Velocities in the (A) Radial Direction and (B) Longitudinal Direction

Table 1. Basic Anthropometric and LV characteristics for the study cohort

	Obese	Normal	
	Weight	Weight	p value
	N = 59	N = 40	
Age (yrs)	47 ± 11	45 ± 11	0.42
Weight (kg)	105 ± 19	69 ± 13	<0.001
Height (m)	1.7 ± 0.1	1.7 ± 0.1	0.65
Body Mass Index (kg/m²)	36.9 ± 6.6	22.9 ± 3.9	<0.001
Total Fat Mass (kg)	44.7 ± 15.4	17.0 ± 3.9	<0.001
Glucose (mmol)	5.1 ± 0.7	5.3 ± 0.9	0.31
Total Cholesterol (mmol)	5.2 ± 0.7	5.2 ± 0.9	0.44
Systolic BP (mmHg)	124 ± 11	121 ± 10	0.10
Diastolic BP (mmHg)	77 ± 9	76 ± 8	0.71
Left Ventricular End Diastolic Volume (ml)	141 ± 22	136 ± 29	0.52
Left Ventricular Stroke Volume (ml)	96 ± 14	86 ± 23	0.03
Left Ventricular Ejection Fraction (%)	68 ± 5	68 ± 5	0.91
Left Ventricular Mass (g)	127 ± 27	106 ± 31	0.003
Sessions of Exercise Per Week (30mins)	1.6 ± 1.5	2.1 ± 1.1	0.42

References

1. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, Hollenbeck A, Leitzmann MF (2006) Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 355 8:763-778
2. Alpert MA (2001) Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *Am J Med Sci* 321 4:225-236
3. Sutton-Tyrrell K, Newman A, Simonsick EM, Havlik R, Pahor M, Lakatta E, Spurgeon H, Vaitkevicius P (2001) Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. *Hypertension* 38 3:429-433
4. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS (2002) Obesity and the risk of heart failure. *N Engl J Med* 347 5:305-313
5. Powell BD, Redfield MM, Bybee KA, Freeman WK, Rihal CS (2006) Association of obesity with left ventricular remodeling and diastolic dysfunction in patients without coronary artery disease. *Am J Cardiol* 98 1:116-120. doi:10.1016/j.amjcard.2006.01.063
6. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH (2004) Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 110 19:3081-3087
7. Scaglione R, Dichiara MA, Indovina A, Lipari R, Ganguzza A, Parrinello G, Capuana G, Merlino G, Licata G (1992) Left ventricular diastolic and systolic function in normotensive obese subjects: influence of degree and duration of obesity. *Eur Heart J* 13 6:738-742
8. Otto ME, Belohlavek M, Khandheria B, Gilman G, Svatikova A, Somers V (2004) Comparison of right and left ventricular function in obese and nonobese men. *Am J Cardiol* 93 12:1569-1572

9. Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Barzilai B, Davila-Roman VG (2004) Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. *J Am Coll Cardiol* 43 8:1399-1404
10. Rider OJ, Francis JM, Ali MK, Petersen SE, Robinson M, Robson MD, Byrne JP, Clarke K, Neubauer S (2009) Beneficial cardiovascular effects of bariatric surgical and dietary weight loss in obesity. *J Am Coll Cardiol* 54 8:718-726. doi:S0735-1097(09)01785-9 [pii] 10.1016/j.jacc.2009.02.086
11. Bella JN, Palmieri V, Roman MJ, Liu JE, Welty TK, Lee ET, Fabsitz RR, Howard BV, Devereux RB (2002) Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. *Circulation* 105 16:1928-1933
12. Schillaci G, Pasqualini L, Verdecchia P, Vaudo G, Marchesi S, Porcellati C, de Simone G, Mannarino E (2002) Prognostic significance of left ventricular diastolic dysfunction in essential hypertension. *J Am Coll Cardiol* 39 12:2005-2011. doi:S073510970201896X [pii]
13. Pavlopoulos H, Nihoyannopoulos P (2009) Regional left ventricular distribution of abnormal segmental relaxation evaluated by strain echocardiography and the incremental value over annular diastolic velocities in hypertensive patients with normal global diastolic function. *Eur J Echocardiogr* 10 5:654-662. doi:10.1093/ejehocard/jep028
14. Peterson LR, Herrero P, Schechtman KB, Racette SB, Waggoner AD, Kisrieva-Ware Z, Dence C, Klein S, Marsala J, Meyer T, Gropler RJ (2004) Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation* 109 18:2191-2196
15. Lamb HJ, Beyersbacht HP, Ouwerkerk R, Doornbos J, Pluim BM, van der Wall EE, van der Laarse A, de Roos A (1997) Metabolic response of normal human myocardium to high-dose atropine-dobutamine stress studied by ³¹P-MRS. *Circulation* 96 9:2969-2977
16. Pluim BM, Lamb HJ, Kayser HW, Leujes F, Beyersbacht HP, Zwinderman AH, van der Laarse A, Vliegen HW, de Roos A, van der Wall EE (1998) Functional and metabolic evaluation of the athlete's

heart by magnetic resonance imaging and dobutamine stress magnetic resonance spectroscopy.

Circulation 97 7:666-672

17. Boudina S, Sena S, Theobald H, Sheng X, Wright JJ, Hu XX, Aziz S, Johnson JI, Bugger H, Zaha VG, Abel ED (2007) Mitochondrial energetics in the heart in obesity-related diabetes: direct evidence for increased uncoupled respiration and activation of uncoupling proteins. *Diabetes* 56 10:2457-2466

18. Masood S, Yang GZ, Pennell DJ, Firmin DN (2000) Investigating intrinsic myocardial mechanics: the role of MR tagging, velocity phase mapping, and diffusion imaging. *J Magn Reson Imaging* 12 6:873-883

19. Duncan MH, Singh BM, Wise PH, Carter G, Alagband-Zadeh J (1995) A simple measure of insulin resistance. *Lancet* 346 8967:120-121

20. Rider OJ, Lewandowski A, Nethononda R, Petersen SE, Francis JM, Pitcher A, Holloway CJ, Dass S, Banerjee R, Byrne JP, Leeson P, Neubauer S (2013) Gender-specific differences in left ventricular remodelling in obesity: insights from cardiovascular magnetic resonance imaging. *Eur Heart J* 34 4:292-299. doi:10.1093/eurheartj/ehs341

21. Petersen SE, Jung BA, Wiesmann F, Selvanayagam JB, Francis JM, Hennig J, Neubauer S, Robson MD (2006) Myocardial tissue phase mapping with cine phase-contrast mr imaging: regional wall motion analysis in healthy volunteers. *Radiology* 238 3:816-826. doi:10.1148/radiol.2383041992

22. Rider OJ, Francis JM, Tyler D, Byrne J, Clarke K, Neubauer S (2013) Effects of weight loss on myocardial energetics and diastolic function in obesity. *Int J Cardiovasc Imaging* 29 5:1043-1050. doi:10.1007/s10554-012-0174-6

23. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z (2004) Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 17 10:1021-1029.

doi:10.1016/j.echo.2004.06.019

24. Sengupta PP, Korinek J, Belohlavek M, Narula J, Vannan MA, Jahangir A, Khandheria BK (2006) Left ventricular structure and function: basic science for cardiac imaging. *J Am Coll Cardiol* 48 10:1988-2001. doi:10.1016/j.jacc.2006.08.030
25. Mizuguchi Y, Oishi Y, Miyoshi H, Iuchi A, Nagase N, Oki T (2008) The functional role of longitudinal, circumferential, and radial myocardial deformation for regulating the early impairment of left ventricular contraction and relaxation in patients with cardiovascular risk factors: a study with two-dimensional strain imaging. *J Am Soc Echocardiogr* 21 10:1138-1144. doi:10.1016/j.echo.2008.07.016
26. Fang ZY, Leano R, Marwick TH (2004) Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. *Clin Sci (Lond)* 106 1:53-60. doi:10.1042/CS20030153
27. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR (2011) Effect of obesity and overweight on left ventricular diastolic function: a community-based study in an elderly cohort. *J Am Coll Cardiol* 57 12:1368-1374. doi:S0735-1097(11)00095-7 [pii] 10.1016/j.jacc.2010.10.042
28. Lamb HJ, Beyersbacht HP, van der Laarse A, Stoel BC, Doornbos J, van der Wall EE, de Roos A (1999) Diastolic dysfunction in hypertensive heart disease is associated with altered myocardial metabolism. *Circulation* 99 17:2261-2267
29. Leite-Moreira AF (2006) Current perspectives in diastolic dysfunction and diastolic heart failure. *Heart* 92 5:712-718. doi:92/5/712 [pii] 10.1136/hrt.2005.062950
30. Boudina S, Sena S, O'Neill BT, Tathireddy P, Young ME, Abel ED (2005) Reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in obesity. *Circulation* 112 17:2686-2695. doi:112/17/2686 [pii] 10.1161/CIRCULATIONAHA.105.554360
31. Perseghin G, Ntali G, De Cobelli F, Lattuada G, Esposito A, Belloni E, Canu T, Costantino F, Ragona F, Scifo P, Del Maschio A, Luzi L (2007) Abnormal left ventricular energy metabolism in obese men with preserved systolic and diastolic functions is associated with insulin resistance. *Diabetes Care* 30 6:1520-1526. doi:dc06-2429 [pii] 10.2337/dc06-2429

32. Rider OJ, Francis JM, Ali MK, Holloway C, Pegg T, Robson MD, Tyler D, Byrne J, Clarke K, Neubauer S (2012) Effects of catecholamine stress on diastolic function and myocardial energetics in obesity. *Circulation* 125 12:1511-1519. doi:CIRCULATIONAHA.111.069518 [pii]
10.1161/CIRCULATIONAHA.111.069518
33. Foell D, Jung B, Germann E, Staehle F, Bode C, Markl M (2013) Hypertensive heart disease: MR tissue phase mapping reveals altered left ventricular rotation and regional myocardial long-axis velocities. *Eur Radiol* 23 2:339-347. doi:10.1007/s00330-012-2613-0
34. Diamant M, Lamb HJ, Groeneveld Y, Endert EL, Smit JW, Bax JJ, Romijn JA, de Roos A, Radder JK (2003) Diastolic dysfunction is associated with altered myocardial metabolism in asymptomatic normotensive patients with well-controlled type 2 diabetes mellitus. *J Am Coll Cardiol* 42 2:328-335
35. Norris SM, Bombardier E, Smith IC, Vigna C, Tupling AR (2010) ATP consumption by sarcoplasmic reticulum Ca²⁺ pumps accounts for 50% of resting metabolic rate in mouse fast and slow twitch skeletal muscle. *Am J Physiol Cell Physiol* 298 3:C521-529. doi:ajpcell.00479.2009 [pii]
10.1152/ajpcell.00479.2009
36. Ibrahim el SH (2011) Myocardial tagging by cardiovascular magnetic resonance: evolution of techniques--pulse sequences, analysis algorithms, and applications. *J Cardiovasc Magn Reson* 13:36. doi:10.1186/1532-429X-13-36
37. Wu L, Germans T, Guclu A, Heymans MW, Allaart CP, van Rossum AC (2014) Feature tracking compared with tissue tagging measurements of segmental strain by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 16 1:10. doi:10.1186/1532-429X-16-10