Myocardial Tissue Phase Mapping Reveals Impaired Myocardial Tissue Velocities in Obesity

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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.

Introduction

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

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

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

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

Methods

Ethics and Study Cohort

This study was a prospective study of ninety-nine healthy subjects (59 obese, 22 male, BMI > 30kg/m^2 and 40 normal weight controls, 18 male, BMI 18.5-24.9 kg/m^2,Table 1). The study was approved by the local ethics committee and therefore has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed written consent was obtained from each subject.

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

Blood tests

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

Bio-Impedance analysis

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

Magnetic Resonance Imaging of the Left Ventricle

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

Tissue Phase Mapping

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

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

Data Analysis

Left Ventricular Morphology

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

Tissue Phase Mapping

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

Statistical Analysis

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

Results

Anthropomorphic Data

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

Left Ventricular Characteristics

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

Tissue Phase Mapping

Systolic Velocity

Radial Systolic Velocity When comparing transmural measurements, there was no significant difference 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-

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

Longitudinal Systolic Velocity In contrast to the radial systolic velocities, peak longitudinal systolic 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 2). However, time-to-peak longitudinal systolic velocity was similar between cohorts (obese 195 ± 145 vs normal 204 ± 165 ms, p = 0.28). Interestingly, although epicardial velocities followed the same pattern with a 11% reduced peak longitudinal systolic velocity (p<0.001) and a similar time-to-peak longitudinal systolic velocity (p>0.30) endocardial time-to-peak longitudinal systolic velocity was delayed in obesity (by 10ms, p<0.001, Figure 3).

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

Diastolic Velocity

Radial Diastolic Velocity When comparing all segments, peak radial diastolic velocity was 13% lower 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-peak radial diastolic velocity was similar between cohorts (obese 496 ± 89 vs normal 496 ± 67 ms, p = 0.90). This pattern was repeated with both endocardial and epicardial peak radial diastolic velocities (epicardial; 7% lower, endocardial; 13% lower in obesity, both p<0.001) and time-to-peak radial diastolic velocities (similar between obese and normal weight groups all p >0.28, Figure 3).

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

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

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

Rotational Velocities

Basal Rotational Velocities There was no significant difference in peak basal systolic clockwise rotational velocity (twist) between the obese and normal weight cohorts (obese 2.3 ± 1.2 vs normal 2.2 ± 0.8 cm/s, $p =0.08$). In contrast, peak diastolic counter-clockwise rotation (untwist) was significantly 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, time-to-peak diastolic untwisting velocity was significantly delayed in obesity (by 53%, obese 307 ± 205 vs normal 200 ± 214 ms, $p < 0.001$).

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

Left Ventricular Torsion and Strain Rate

When comparing the obese and normal weight cohorts, there was no significant difference in either peak 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 radial strain rate (obese 46 ± 12 vs normal 52 ± 19 ms, $p =0.07$). In contrast, although peak diastolic

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), time-to-peak diastolic radial torsion was significantly delayed in obesity (obese 103 ± 45 vs normal 48 ± 53 ms, p <0.001).

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

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

Discussion

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

Systolic Function in Obesity

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

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

Diastolic Function in Obesity

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

Pattern of Change Compared to Other Myocardial Disease Processes

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

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

Potential Mechanisms Behind Functional Changes in Obesity

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

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

Comparison to Other CMR Sequences

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

Conclusion

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

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

Figure Legend

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

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

	Obese	Normal 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

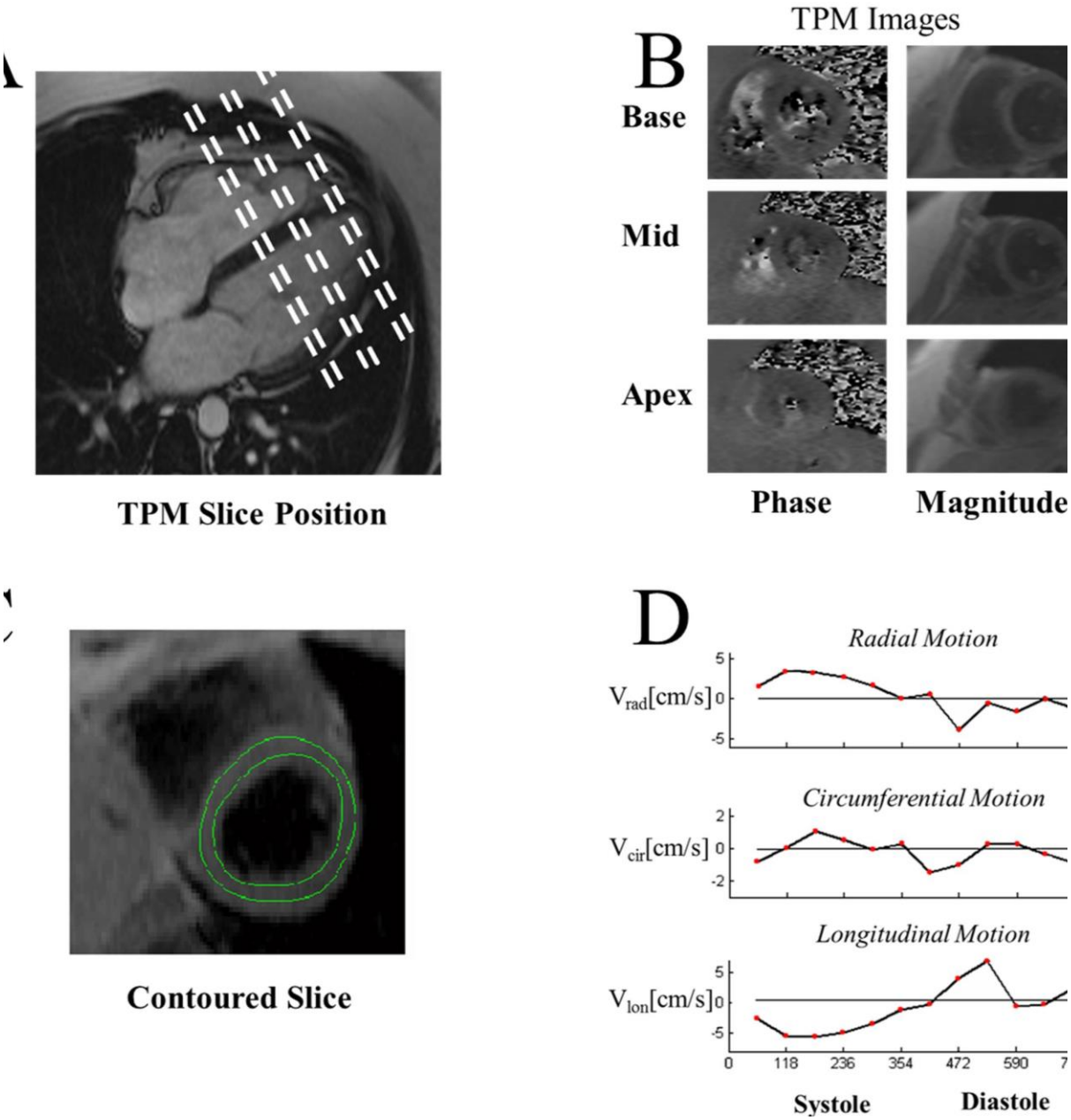
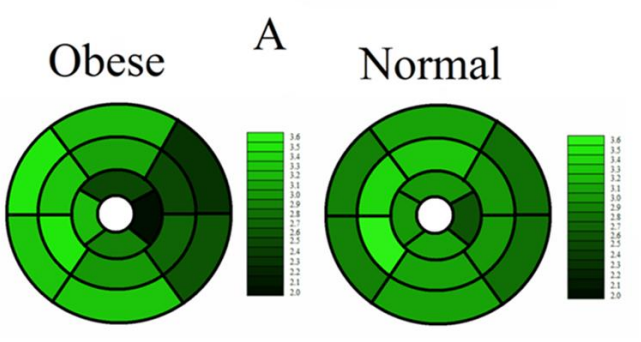
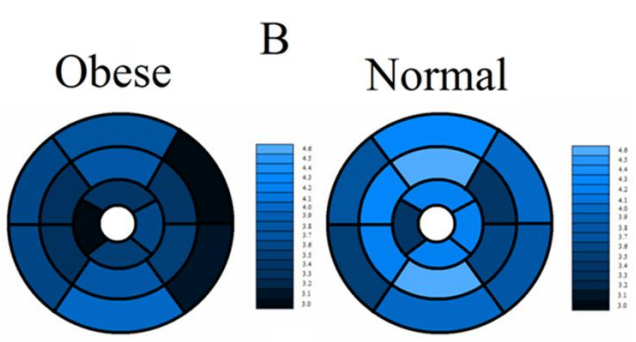


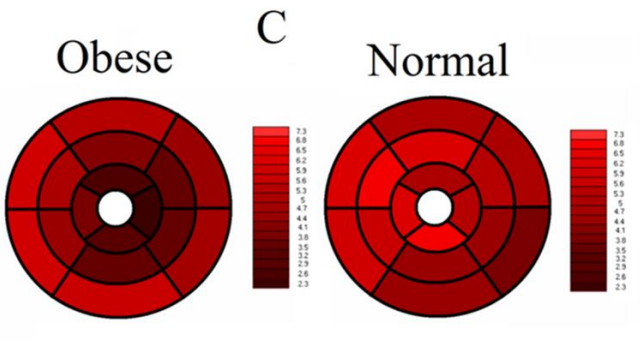
Figure 1. (A) Example slice positions relative to Horizontal Long Axis view, (B) TPM phase and magnitude images at the base, mid-ventricular and apical level, (C) Example of epicardial and endocardial contours on a basal slice and (D) An example of the generated radial, circumferential and longitudinal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



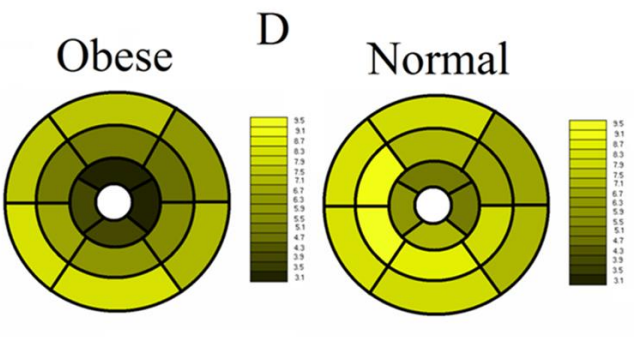
Radial Systolic Velocity



Radial Diastolic Velocity



Longitudinal Systolic Velocity



Longitudinal Diastolic Velocity

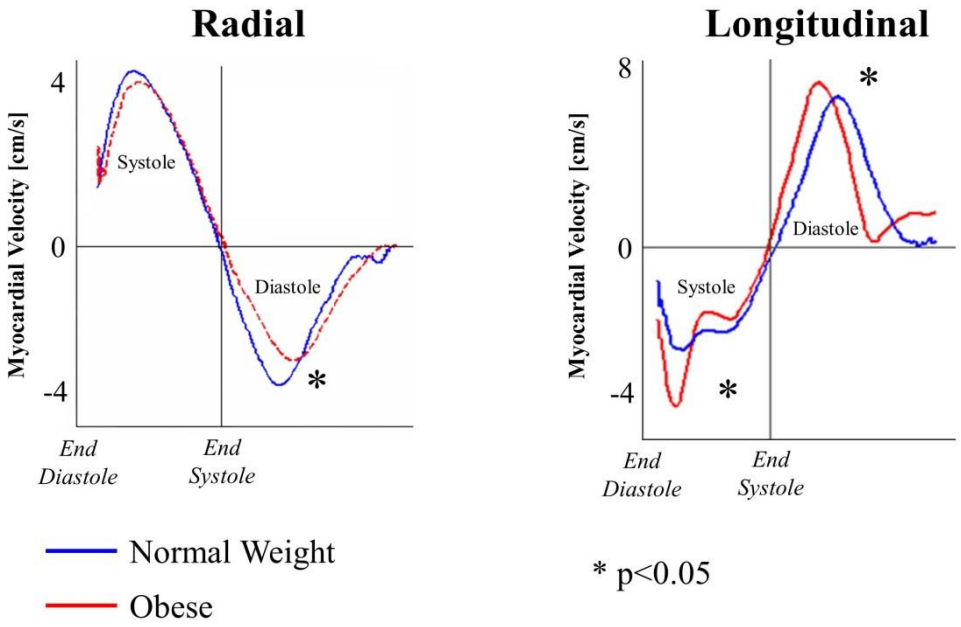


Figure 3. The Effect of Obesity on Global Myocardial Velocities in the (A) Radial Direction and (B) Longitudinal Direction