

# Assessment of segmental left ventricular thickening in diabetic type II obese patients with normal myocardial perfusion scan

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## Abstract

**Objective:** The aim of this study is to investigate whether gated single photo emission tomography (gSPET) can be used to detect subclinical left ventricular systolic dysfunction (LVSD) in obese diabetic type II patients. **Subjects and Methods:** We retrospectively reviewed gSPET images of 190 patients with diabetes mellitus type II (DM II) (137 females and 53 males) with normal myocardial perfusion and normal ejection fraction (EF). Standardized twenty segment polar maps of thickening and motion were generated. Correlation between body mass index (BMI) and thickening for each segment was performed. **Results:** Statistically significant results were reported in female patients including: negative correlation between BMI and EF (-0.19, P=0.03). End diastolic volume (EDV) also significantly increased with increasing BMI (0.25, P<0.01). There was also statistically significant negative correlation between septal thickening and BMI segment 15 (-0.19, P=0.02), segment 16 (-0.22, P=0.01), segment 18 (-0.20, P=0.01), segment 19 (-0.25, P=0.003), segment 20 (-0.2, P=0.02). No statistical significant correlation was found between thickening and BMI in male patients. **Conclusion:** This is the first time where thickening as measured by gSPET has been used to demonstrate subclinical LVSD in DM II obese patients. The relationship between gender and obesity on cardiovascular function and structure needs further investigations.

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## Introduction

Obesity is a growing epidemic in many parts of the world; it is associated with an increased risk of developing heart failure [1], as well as an increased overall risk of death [2]. The adverse effects of obesity on myocardial structure and function could be direct, due to increased demand of cardiac output, or indirect because of the high prevalence of coexisting disorders, such as coronary artery disease (CAD), dyslipidemia, DM II and hypertension (HTN) [3-4].

Obesity is associated with a wide range of cardiac abnormalities including increased left ventricular mass, LV hypertrophy, left ventricular diastolic dysfunction (LVDD), increased end diastolic volume (EDV), increased end systolic volume (ESV) and increased cardiac output [5-9]. The relationship between LV systolic function (LVSF) and obesity, on the other hand is controversial. While several studies found that depressed LV ejection fraction (EF) was independently and positively associated with body mass index (BMI) [10-16], other studies found preserved systolic LV function and LVEF in obese subjects [17-18]. In a large systematic evaluation of the relation between BMI and the LV structure and function in subjects with normal myocardial perfusion studies Dorbala et al. (2006) found that although LV enlargement was evident in mild degrees of obesity, LVEF was not adversely affected even in severe degrees of obesity [19]. Powell et al. (2006) found no association between LV systolic function (LVSF) as assessed by echocardiographic measurement of LV (fractional shortening and ratio of fractional shortening to ES wall stress) and obesity in a large cohort of patients with normal coronary angiography [18]. In Contrast, others reported an association between obesity and LVS dysfunction (LVSD) [19-24].

The contradiction between these reports could be related to heterogeneous groups of patients included in these studies particularly in relation to diabetes mellitus and to differences in techniques applied to measure LVSF. Obesity and diabetes are entwined and it is difficult to evaluate their isolated or independent effect on LV structure and function [25-26], in addition, insulin resistance has been associated with LV remodeling and dysfunction independently of BMI [19, 27].

Furthermore; the conventionally used assessment of LVEF and fractional shortening of

LV are likely insensitive to detect subclinical alterations in LVSF [28]. Echocardiographic studies showed that tissue Doppler imaging and myocardial strain provide a more reliable and reproducible measurement of regional and global LVSF [28]. Regional LVSF can also be assessed by ECG-gated single photon emission tomography (gSPET) where segmental systolic wall thickening (SWT) is considered an objective and reproducible SPET measure of regional LVSF [29]. Wall thickening has also demonstrated good correlation with longitudinal strain measured by echocardiography [29-32]. Therefore echocardiographic strain and SPET WT can be considered as early markers of impaired LVSF.

In theory, if subclinical LVSD can be diagnosed early in the disease process, prevention of further deterioration is possible and likely to be more successful than waiting for EF to be depressed, which may be too late for treatment.

In this study we aimed to evaluate the effect of obesity in patients with DM II and no evidence of CAD on regional LVSF using WT.

## Subjects and Methods

### Study population

We retrospectively evaluated patients with DM II who were referred for myocardial perfusion scintigraphy from June 2010 until June 2013. The study included 190 DM II patients (137 females and 53 males); average age was 57.9 years ( $\pm 9.9$  years) with age range from 34 to 85 years. Only patients with normal myocardial perfusion scintigraphy and preserved EF ( $EF \geq 50\%$ ) were enrolled. Patients known to have prior CAD, heart failure, angina, amyloidosis, sarcoidosis, atrial fibrillation or valvular heart disease were excluded a priori. Patients with electrocardiographic (ECG) evidence of left or right bundle branch block or patients with significant LV hypertrophy by echocardiography (septal thickness of  $\geq 1.4$ cm) were also excluded. Patients who developed coronary events in the three years following myocardial perfusion scintigraphy were also excluded based on their chart review. Medical records were reviewed for the presence of hypertension and DM II. Patients' height and weight were recorded. This study was approved by the Ethical Committee review board at Jordan University Hospital. Subjects were classified based on their BMI (weight in kilograms divided by height in meters squared) as normal ( $18.5$  to  $<25$ kg/m<sup>2</sup>), overweight ( $\geq 25$  and  $<30$ kg/m<sup>2</sup>), obese ( $\geq 30$  and  $<35$ kg/m<sup>2</sup>), or severely obese ( $\geq 35$ kg/m<sup>2</sup>).

### Myocardial perfusion SPET and stress protocol

All patients underwent standard two days gated stress-rest technetium-99m hexakis 2-methoxyisobutyl isonitrile (sestamibi) (10MBq/kg) myocardial perfusion SPET. Attenuation correction software was not used. Subjects underwent either standard symptoms limited Bruce treadmill tests or adenosine stress test (140 $\mu$ g/kg/min for 6 minutes with injection of the radiopharmaceutical at the end of the third minute.

Sixty-four projections (40 seconds each) were acquired with a 64 $\times$ 64 matrix over a 180° circular orbit from right anterior oblique 45° view to the left posterior oblique 45° view using a single head gamma camera Meridian, Philips, USA, equipped with low energy high resolution collimator and set at 140keV $\pm$ 10%. ECG-gating was based on 8 frames per R-R interval and a gated tolerance of 60%. All data were processed at a single workstation (Pegasys, write details) using a commercial software QPS/QGS developed by Cedars-Sinai (Los Angeles, USA). The gated SPET projection data sets were constructed using an iterative OSEM (number of iterations and subsets) algorithm with Butterworth "post-filtering" (cut-off 0.4cycles/cm and order 8 for summed data; 0.55cycles/cm and order 8 for gated data).

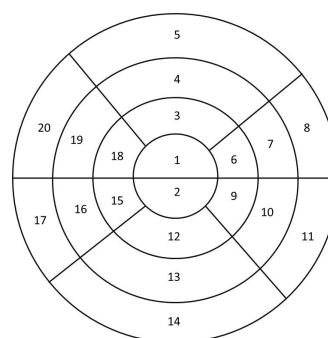


Figure 1. Standardized 20 segment polar map of left ventricle.

### Image analysis and data interpretation

All perfusion images were visually interpreted by an expert nuclear medicine physician (A.A). The Cedars-Sinai quantitative gSPET software (QGS, Cedars Sinai Inc., Los Angeles, California) was applied to reconstructed short-axis tomograms to assess rest global left function LVEF and regional segmental thickening and motion. Wall thickening is expressed as the percentage of end diastolic WT and wall motion is expressed in millimeters, both were registered for a 20-segment LV model. Rest end systolic volume (ESV), rest end diastolic volume (EDV) and LVEF were also recorded. The entire process was expressed automatically without manual intervention.

### Statistical analysis

Statistical analysis was performed using SPSS version 17 as well as Pearson correlation between continuous variables. Statistical significance of correlation was obtained using two tailed T test. Statistical significance was set at values 0.05 or less. Anova test was done to test for correlations between different weight subgroups and regional wall motion or WT.

## Results

Out of the 190 patients studied, there were 8 patients with normal weight (3 females and 5 males), 53 overweight patients (36 females and 17 male), 63 obese patients (46 females

and 17 male) and 66 morbidly obese patients (52 female patients and 14 male patients). There were 154 patients with hypertension and 36 patients without hypertension. Table 1 describes patients' characteristics in detail.

**Table 1.** Distribution of patients according to gender, BMI and presence of hypertension.

Characteristics	BMI*			
	<25	25-29.9	30-34.9	≥35
<b>Females (137)</b>	5	36	45	51
Mean age (years)	46±13	58±10	58±10	59±9
Hypertension	67%	69%	87%	92%
<b>Males (53)</b>	5	17	16	15
Mean age (years)	58±12	53±11	52±6	
Hypertension	60%	82%	69%	87%

\*BMI: Body Mass Index

We found that EDV and ESV were increased, while EF was decreased with increasing BMI only in female patients, Table 2 summarizes the correlation between BMI and EF, EDV and ESV as measured by gSPET.

There was a statistically significant negative correlation between BMI and segmental motion at the mid and proximal anteroseptal segments of LV [segments 4 (-0.16, P=0.03), segment 5 (-0.143, P=0.04), segment 19 (-0.21, P<0.01), segment 20 (-0.15, P=0.04)] and distal lateral segments [segment 6 (-0.17, P=0.02) and at the distal inferolateral segment [segment 9 (-0.15, P=0.01)]. When segmental motion was analyzed based on gender, female patients had statistically significant negative correlation at mid anteroseptal segment (segment 19; -0.19, P=0.03).

Thickening also correlated negatively with BMI at mid-septal segments [segment 16 (-0.23, P<0.01) and segment 19 (-0.18, P=0.01)] in all patients, however this was evident only in female patients at gender subgroup analysis [segment 15 (-0.19, P=0.02), segment 16 (-0.22, P=0.01), segment 18 (-0.20, P=0.01), segment 19 (-0.25, P=0.003), segment 20 (-0.2, P=0.02)]. Figure 2 shows segment 15 as an example of negative correlation between BMI and WT in female patients.

There was no statistically significant difference between segmental wall motion or thickening among BMI subgroups (normal, overweight, obese and morbidly obese) but there was a trend towards decreased thickening as BMI group increased, this can be explained by using a relatively small sample size. There was no statistically significant correlation between the presence of hypertension and segmental motion or thickening for all patients and for each gender subgroup.

**Table 2.** Correlation between weight and BMI versus ejection fraction, end diastolic volume and end systolic volume

Ejection Fraction		
Subjects	Weight	BMI#
All patients	-0.25, P value <0.01	NS*
Female patients	NS*	-0.19, P value 0.03
Male patients	NS*	NS*
End Diastolic Volume		
Subjects	Weight	BMI#
All patients	0.43, P value <0.01	NS*
Female patients	0.40, P value <0.01	0.25, P value <0.01
Male patients	0.28, P value 0.046	NS*
End Systolic Volume		
Subjects	Weight	BMI#
All patients	0.52, P value <0.01	NS*
Female patients	0.36, P value <0.01	0.24, P value <0.01
Male patients	NS*	NS*

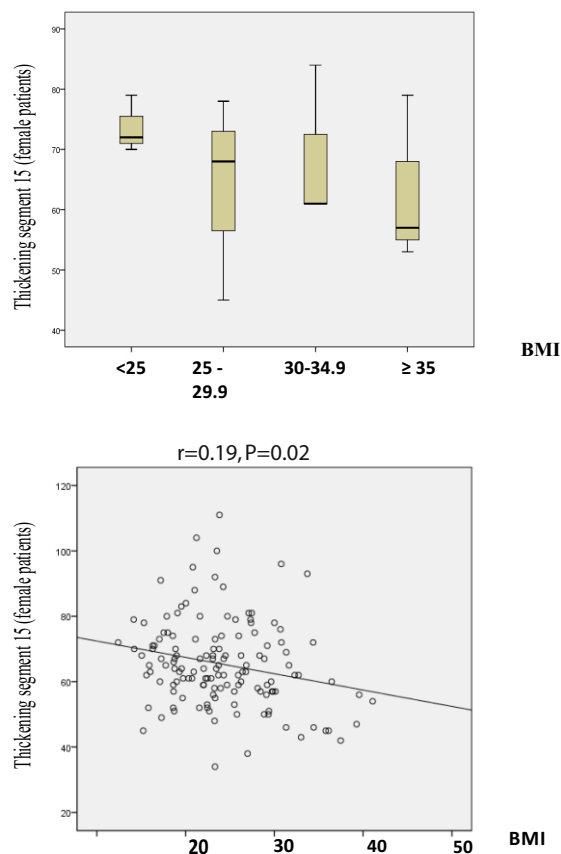
\*NS: not significant, #BMI: Body Mass Index.

## Discussion

Obesity is one of the epidemics of our time. In the United States, the prevalence of obesity among adults over the age of 20 is approximately 36% [33]. Obesity has been recognized as an independent risk factor for heart failure, accounting for 14% in female and 11% in male patients with heart failure after adjusting for other risk factors like HTN, DM, valve disease, and myocardial infarction [1]. In addition, obesity has been linked to a wide range of cardiovascular dysfunctions ranging from hyperdynamic circulation to principally increased LVEDV, LVESV, LV mass and diastolic dysfunction as have been consistently demonstrated in several papers [1-24]. The effect of obesity on EF and on LVSF is however controversial [19]. Furthermore, obese patients have been demonstrated to have subclinical LV dysfunction even in the presence of normal EF. Deng et al (2010) have demonstrated significantly reduced apical torsion in obese patients using velocity Vector Imaging [34].

Another study demonstrated that increasing levels of obesity showed differences in myocardial velocity and strain

index even when conventional echocardiogram gives normal values of EF [28]. Several previous studies which evaluated the effect of obesity on LV function did not exclude CAD as a confounding factor as we did [1-22]. Others have developed a completely automated, quantitative algorithm (QGS) for the measurement of regional motion and thickening from 3-dimensional gated myocardial perfusion SPET.



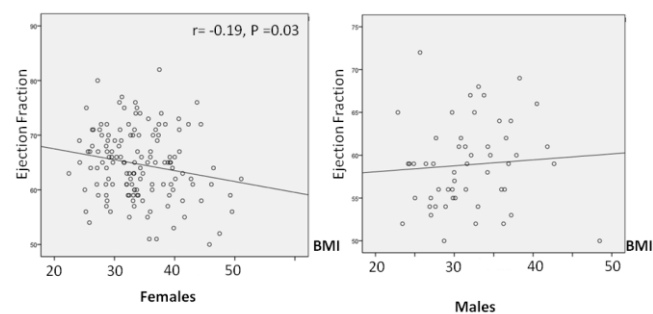
**Figure 2.** Panel A: Whiskers box plot demonstrating tendency towards decreasing thickening with increasing BMI group in female patients at inferoseptal segment (segment 15), no statistically significant difference was however found between different groups. Panel(B): negative linear correlation between BMI and thickening in female patients at inferoseptal segment (segment 15).

Conventionally, gated myocardial perfusion images are assessed for EDV, ESV and EF, in addition thickening and motion of LV are scored (from 0 to 5) against reference population. This approach is inherently affected by the limited spatial resolution of SPET (particularly when measuring ESV) therefore overestimating EF in patients with small LV particularly female patients. Applying segmental analysis of motion and thickening is expected to offer better analysis of the correlations between LV motion and thickening on one hand and BMI on the other hand, independently of limited SPET spatial resolution. The range of motion and thickening used to define different scores may limit the sensitivity of these parameters in detecting subclinical dysfunction. In our study, we have used motion in millimeters and thickening expressed in percentage rather than the conventio-

nally used scores in the aim of increasing accuracy of LVSD detection [35, 36].

Left ventricular WT, as measured by gSPET, has been demonstrated to be a highly sensitive tool to detect early myocardial systolic dysfunction, it also proved to be an independent predictor of all cause mortality regardless of EF, in addition, wall thickening has been proven to correlate with longitudinal strain measured by echocardiography which is a very sensitive tool to detect early LVSD [29-32]. No studies have been performed to assess the role of LVWT in detecting subclinical LVSD in obese diabetic II patients.

Our results demonstrated reduced WT and motion by increasing BMI in female DM II patients; this was also manifested globally by reduced EF when BMI was increasing (Figure 3). In addition, increasing BMI resulted in statistically significant increase of EDV or ESV; this was evident only in female patients (Table 2). We could not find a statistically significant effect of BMI on segmental motion and segmental WT or EF in male DM II subjects. Regional LVSD, as demonstrated by our results, was more evident using segmental WT rather than motion. gSPET was better suited for the assessment of WT since it is dependent on count-density-WT relationship measurements whereas motion measurements may be partially affected by the translational motion of the heart [37].



**Figure 3.** Negative linear correlation between ejection fraction and BMI in female patients while there is no statistically significant correlation between BMI and ejection fraction in male patients.

Gender differences in LV remodeling in relation to obesity have been investigated by several authors. Recently, regional LVSD was demonstrated only in women with myocardial stentosis using regional LV strain while affected wall segments were not identified [38]. Moreover, it has been recently demonstrated that myocardial metabolic response to obesity differs among genders, whereas only females demonstrate increase in myocardial blood flow and oxygen consumption due to increased myocardial fatty acid oxidation which is less efficient than glucose oxidation [39]. Whether this specific metabolism in obese female patients is related to the observed regional LVSD needs further investigation. Our paper included a larger number of female DM II patients; this may have also resulted in statistical bias towards the female gender.

*In conclusion*, to our knowledge, this is the first study that looks at LV wall thickening to measure regional LV systolic function in diabetic II obese patients by gated SPET. The relationship between gender and obesity and their effects on car-

diovascular function and structure differences need further investigation.

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The authors of this study declare no conflicts of interest

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