7-31-2013

Association between obesity and infarct size: insight into the obesity paradox.

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As submitted to:

International Journal of Cardiology

And later published as:

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Volume 167, Issue 2, pages: 604-6, July 31, 2013

DOI: 10.1016/j.ijcard.2012.09.230

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Word count: 1,971 words excluding abstract, tables, figures and references

Key words: Obesity paradox, myocardial infarction, troponin, coronary heart disease, NSTEMI, STEMI.

Abbreviations:

BMI = body mass index

CHD = Coronary heart disease

CPK = Creatinine phosphokinase

CV = Cardiovascular

EAT = Epicardial adipose tissue

MI = myocardial infarction

NSTEMI = Non-ST elevation myocardial infarction

PAT = Pericardial adipose tissue

STEMI = ST elevation myocardial infarction

WC = Waist circumference

Abstract:

Background: In patients with coronary heart disease, being overweight or obese is associated with better outcomes, a phenomenon known as the 'obesity paradox'. Despite the high prevalence of obesity in the United Sates, its effects on infarct size are largely unexplored.

Methods: Prospective cross-sectional study of 102 consecutive patients admitted with acute myocardial infarction (MI). Standardized forms were used to collect data on body mass index (BMI), waist circumference (WC), cardiovascular risk factors, and medications. Peak troponin I and creatinine phosphokinase (CPK) were used to estimate infarct size. Epicardial and pericardial fat were measured by echocardiography. We used univariate and multivariate analyses to assess whether obesity was associated with infarct size. Correlations between BMI, WC and cardiac fat with cardiac biomarkers were also performed.

Results: Mean age was 62±12 years, and 55% were men. Obesity was diagnosed in 69%. On multivariate analysis, obesity was associated with *greater* infarct size in non-ST elevation MI (p=0.02). A *positive* correlation was observed between BMI and peak troponin I (rho=0.24, p=0.03), and both, BMI and WC had a *positive* correlations with CPK levels (rho=0.28, & rho=0.28, both p=0.02). However, in ST elevation MI, obesity was associated with *smaller* infarct size (p=0.05). Epicardial fat + pericardial fat had a *negative* correlation with peak CPK levels (rho=-0.36, p=0.05).

Conclusions: We observed an opposite association between obesity and infarct size depending on the type of MI. These results were unexpected and may provide insight into the pathophysiology of the obesity paradox. (Word count: 244)

Introduction:

Obesity has become the epidemic of our time. Studies using body fat to diagnose obesity estimate that 1 of every 2 people are obese [1, 2]. Obesity contributes to the development of several cardiovascular (CV) risk factors, including hypertension, diabetes, metabolic syndrome, dyslipidemia, and obstructive sleep apnea, and may be an independent risk factor for coronary heart disease (CHD) [3]. However, large epidemiologic studies have shown that, compared to normal weight people, overweight and obese subjects with CV diseases, including CHD and following an acute myocardial infarction (MI), have better outcomes [4], a phenomenon known as the "obesity paradox" [4-8].

It is well accepted that cardiac biomarkers reflect myocardial damage. Of the several cardiac biomarkers, troponin I best reflects infarct size [9, 10], showing an excellent correlation with infarct size, as measured by cardiac magnetic resonance ($r=0.84$), and has independent prognostic value [9-11].

Despite obesity being prevalent in patients with MI, its effects on infarct size are largely unexplored. The aim of this study was to examine associations between obesity and cardiac fat with infarct size estimated by peak troponin I and creatinine phosphokinase (CPK) levels.

Methods:

Study design and subject selection

A prospective cross-sectional study of 102 consecutive patients aged 30 to 89 years who were admitted to the coronary care unit from March 2010 to March 2011 with the diagnosis of MI was performed. We excluded patients with recent cocaine use, severe congestive heart failure (ejection fraction <20%), on hemodialysis, or with severe psychiatric conditions (unable to sign consent). Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Einstein Healthcare Network Institutional Review Board. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [12].

Anthropometric measurements and obesity definition

Standardized forms were used to collect data on anthropometric variables. Body weight was measured with an electronic load cell scale to the nearest 0.01 kg. Height was measured to the nearest 0.1 cm using a fixed stadiometer. Waist circumference (WC) was determined using a measuring tape positioned at the high point of the iliac crest at the end expiration with the tape snug but not compressing the skin. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Obesity was defined according to American Heart Association as a BMI $\geq$30 kg/m^2 and/or WC $\geq$88 cm in women and $\geq$102 cm in men [3].

Abstraction of clinical data

Standardized forms and medical records were used to obtain demographics and to determine the presence/absence of CV risk factors. Hypertension, diabetes, dyslipidemia, history of CHD and congestive heart failure were documented if self-reported by the patient or previously recorded on medical records, or if the patients were on medical therapy for those conditions. We further collected data on family history of premature CHD disease, smoking (current/former) and time of onset of chest pain. Screening for sleep apnea was performed by using the modified Berlin questionnaire [13]. Acute MI, non-ST elevation MI (NSTEMI), and ST elevation MI (STEMI) were defined according to American Heart Association and American College of Cardiology recommendations [14].

Laboratory data collected included complete blood count, fasting basic metabolic profile, fasting lipid profile and cardiac biomarkers (troponin I and CPK). We recorded peak troponin I and CPK levels as surrogates of infarct size as previously described [9-11]. At the time of admission, medications were recorded, including the use of antihypertensives, diuretics, nitrates, antiarrhythmics, diabetes medications, statins or any other lipid lowering therapy, antiplatelet and anticoagulation therapy.

Echocardiographic and angiographic data

Transthoracic Doppler echocardiography was performed and reported according to the American Society of Echocardiography guidelines [15]. Cardiac fat, including epicardial adipose tissue (EAT), pericardial adipose tissue (PAT) and EAT plus PAT (EAT+PAT)

were measured by transthoracic echocardiography by a single operator (ARC) averaging 3 consecutive beats at end-systole in the parasternal long axis view [16].

Intraobserver variability was performed by re-measuring 10 randomly selected patients one month later ($r=0.97$, $p<0.0001$). All measurements were performed blinded to clinical data of the patients. Angiographic data, including number of diseased vessels, as well as culprit vessel, were obtained from cardiac catheterization reports.

Statistical analyses

Data are reported as mean ± SD for continuous variables, and number and (%) for categorical variables. This study was designed to detect a difference of 4 ng/mL in peak troponin I between obese and non-obese subjects with 80% power and a two-tail $\alpha=0.05$. To assess baseline differences by type of MI and obesity status we used Students t-test for continuous variables and Chi^2 or Fishers exact test for categorical variables. We tested for normal distribution across the recorded variables, and we used the logarithm of peak troponin I and creatinine phosphokinase (CPK) due to the skewness of these continuous variables. Non-parametric correlations (Spearman) were performed to establish the association between BMI, WC, and cardiac fat with cardiac biomarkers. Due to significant difference in the peak troponin and CPK levels between NSTEMI and STEMI, analyses were reported separately. Two-tail p-values <0.05 were considered significant in advance. We performed univariate analyses to identify predictors of infarct size estimated by peak troponin I and CPK levels (p-value for inclusion <0.10). Multivariate analyses were performed to identify independent predictors of infarct size after adjustment for age, sex, race, traditional cardiovascular risk factors, obstructive

sleep apnea, ejection fraction, three vessel disease, and time of onset of chest pain (p-value $\leq$0.05). Analyses were performed using JMP version 10.0 (SAS Institute, Cary, NC).

Results:

We enrolled 102 subjects (**Table 1**) of whom 73 (71.5%) had NSTEMI. Mean age of the sample was 61±12 years, and 56 (55%) were men. Sixty-one percent were African American, 21% Caucasian, 12% Hispanic, and 6% of other race. Obesity was present in 69%. Comparing STEMI with NSTEMI (**Table 1**), those with STEMI were younger (58±12 vs. 63±12 years, p=0.05), had a lower prevalence of previously diagnosed CHD (14 vs. 45%, p=0.002), congestive heart failure (0 vs. 13%, p=0.04), and more PAT (8±3.1 vs. 6.6±2.8mm, p=0.05).

Association between obesity and infarct size in NSTEMI patients

Baseline characteristics, as well as CV risk factors and cardiac biomarkers between obese and non-obese subjects with NSTEMI are shown in **Table 2A**. Compared to non-obese subjects, those with obesity were more likely to be women (70 vs. 42%, p=0.02) and diabetic (57 vs. 22%, p=0.004), had a high probability of having obstructive sleep apnea (68 vs. 13%, p<0.0001), and had *higher* peak troponin I (23.6±31 vs. 17.8±37ng/mL, p=0.04) and CPK levels (590±549 vs. 334±274U/L, p=0.05) -**Figure 1A**.

Significant univariate predictors for infarct size estimated by peak troponin I were hypertension (p=0.01), obesity (p=0.03) and possibly race (p=0.09), all of which were associated with *higher* troponin I. On multivariate analysis, obesity (p=0.02) remained a significant predictor of *higher* peak troponin I. Hypertension (p=0.01) and obesity (p=0.04) were significantly associated with *higher* peak CPK levels (**Table 3A**). On

multivariate analysis both obesity (p=0.02) and hypertension (p=0.02) remained significant predictors for *higher* peak CPK (**table 4A**).

Correlations between BMI, WC, and cardiac fat with cardiac biomarkers are shown in **Table 5A**. BMI had a significant *positive* correlations with peak troponin I (rho=0.24, p=0.03) and CPK (rho=0.28, p=0.02), while WC had a significant *positive* correlation with peak CPK (rho=0.24, p=0.05).

Association between obesity and infarct size in STEMI patients

Baseline characteristics, as well as CV risk factors and cardiac biomarkers between obese and non-obese subjects with STEMI are shown in **Table 2B**. Compared to non-obese subjects, those with obesity had more EAT (7.1±2.2 vs. 4.9±1.9mm, p=0.01), and EAT+PAT (15.8±3.8 vs. 11.5±4.7mm, p=0.03), and had *lower* peak troponin I (104±141 vs. 182±114ng/mL, p=0.02) -**Figure 1B**.

Significant univariate predictors for infarct size estimated by peak troponin I were age (p=0.05) which was associated with *higher* peak troponin I, while obesity (p=0.06), EAT (p=0.05), and EAT+PAT (p=0.07) were associated with *lower* peak troponin I. On multivariate analysis, only obesity (p=0.02) remained as a significant predictor for *lower* peak troponin I. For peak CPK levels, age (p=0.06), history of CHD (p=0.04) and diabetes (p=0.06), were significant predictors of *higher* peak CPK (**Table 3B**), while EAT+PAT (p=0.05) was associated with *lower* peak CPK. On multivariate analysis none

of those remained significant, though there was a trend for diabetics (p=0.08) to have *higher* peak CPK (**Table 4B**).

Correlations between BMI, WC, and cardiac fat with cardiac biomarkers are shown in **table 5B**. A trend towards a *negative* correlation was observed between EAT and EAT+PAT with peak troponin I (rho=-0.33, p=0.08, and rho=-0.34, p=0.07, respectively), while a significant *negative* correlation was observed between EAT+PAT with peak CPK (rho=-0.36, p=0.05). A trend towards a *negative* correlation was also observed between EAT and PAT with peak CPK levels (rho=-0.31, p=0.10, and rho=-0.34, p=0.06, respectively).

Discussion:

The main finding of our study is that obesity has a significant and independent association with infarct size at the time of acute MI. Interestingly, obesity was associated with *greater* infarct size in patients with NSTEMI, while in patients with STEMI it was associated with *smaller* infarct size. To our knowledge, this is the first study to report an association between cardiac fat and infarct size. We also observed that EAT+PAT is associated with *smaller* infarct size among STEMI patients.

There are only a few small studies that have examined the association of obesity on infarct size. Pingitore, et al, performed cardiac magnetic resonances in 89 patients after their first MI (at least 3 months old) to assess the extent of MI size. They observed a *smaller* infarct size in obese patients. In should be noted that >80% of their population were STEMI, and these findings are similar to our STEMI group [17]. In another study, Iglesias Bolanos, et al, studied the association between total and central obesity on infarct size in 40 men at the time of MI. Both BMI (r=0.43) and WC (r=0.47) showed a significant *positive* correlation with CPK (measured as AUC) [18]. These correlations are similar to our group of NSTEMI patients. It is important to note that Igleasias Bolanos study did not distinguished between STEMI and NSTEMI that in our study was noted to be an *effect-modifier*, meaning that obesity had opposite associations with infarct size by type of MI, and in fact, the interaction between BMI (but not WC) with peak troponin I by type of MI was statistically significant (p=0.005).

Furthermore, we believe this is the first study looking at the association of cardiac fat measured by echocardiography with infarct size. We observed that EAT+PAT was associated with *smaller* infarct size in STEMI patients. Much recent work has focused on the pathophysiology of cardiac fat in cardiovascular disease, and our findings though interesting, need to be replicated in larger studies.

Strengths and limitations

Strengths of our study include the careful adjustment for potential confounders, including obstructive sleep apnea, which is rarely accounted for in obesity studies. In addition, we excluded other potential confounders, including patients on hemodialysis and severe congestive heart failure. Limitations of our study include a relatively small sample size, especially in the STEMI group (28.5% of MI), which could have limited our power to detect other possible associations with infarct size. Another potential limitation is the use cardiac biomarkers to estimate infarct size, instead of actually measuring infarct size by cardiac magnetic resonance or other novel technologies. However, recent work has shown that a single measurement of peak troponin I has an excellent correlation with infarct size [9-11].

Conclusions

We observed significant associations between obesity and infarct size. Interestingly, the direction of these associations varied by type of MI. While obesity was associated with *greater* infarct size in NSTEMI patients, obesity was associated with *smaller* infarct size

in STEMI. These results were unexpected and may provide insight into the pathophysiology of the obesity paradox.

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Figure legends

Figure 1A. Cardiac biomarkers by obese status in NSTEMI patients.

Figure shows in the Y axis (log) peak troponin I and (log) peak CPK and in the X axis obese vs. non-obese patients with NSTEMI. There is a significant difference in cardiac biomarkers with *higher* levels in the obese group.

Figure 1B. Cardiac biomarkers by obese status in STEMI patients.

Figure shows in the Y axis (log) peak troponin I and (log) peak CPK and in the X axis obese vs. non-obese patients with STEMI. There is a significant difference in cardiac biomarkers with *lower* levels in the obese group.

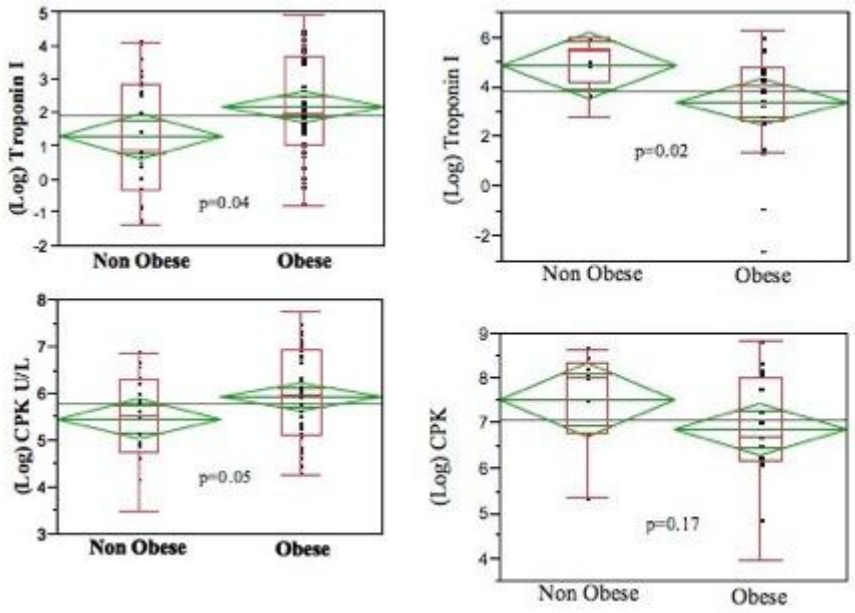

Table 1 Baseline characteristics for all patients, and by type of AMI

Variable	All n = 102	STEMI n = 29	NSTEMI n = 73	+p-value
Age, years	61.9 ± 12	58 ± 12	63 ± 12	0.05
Sex, men	56 (55)	19 (65)	37 (51)	0.17
Race, %				
African-American	62 (61)	18 (62)	44 (60)	
Caucasian	22 (21)	7 (24)	15 (21)	0.79
Hispanic	12 (12)	2 (7)	10 (14)	
Other	6 (6)	2 (7)	4 (5)	
*Obese, %	70 (69)	20 (69)	50 (68)	0.96
BMI, km/m^2	30.1 ± 6.7	29.8 ± 6	30.3 ± 7	0.71
Waist circumference, cm	102 ± 17	102 ± 15	102 ± 18	0.87
Epicardial Fat, mm	6.2 ± 2.2	6.4 ± 2.3	6.1 ± 2.2	0.52
Pericardial Fat, mm	7.0 ± 2.9	8.0 ± 3.1	6.6 ± 2.8	0.05
Epicardial + Pericardial Fat, mm	13.2 ± 4.6	14.4 ± 4.5	12.7 ± 4.5	0.10
Hypertension, %	94 (93)	27 (93)	67 (93)	0.99
Diabetes, %	43 (43)	10 (34)	33 (46)	0.29
Dyslipidemia, %	81 (80)	20 (69)	72 (85)	0.07
Smoking, %	47 (47)	12 (41)	35 (48)	0.50
Family history of coronary disease, %	52 (51)	14 (48)	38 (52)	0.73
History of coronary artery disease, %	37 (36)	4 (14)	33 (45)	0.002
Congestive heart failure, %	9 (9)	0 (0)	9 (13)	0.04
Obstructive sleep apnea, %	55 (54)	18 (62)	37 (51)	0.29
Ejection fraction, %	45 ± 12	44.6 ± 12	45.4 ± 12	0.78
Onset of chest pain to peak enzyme, hrs.	16.7 ± 16	12 ± 4.6	18 ± 19	0.007
Triple vessel disease^, %	33 (34)	6 (21)	27 (39)	0.09
Creatinine, mg/dL	1.3 ± 0.4	1.39 ± 0.4	1.25 ± 0.4	0.18
+Peak troponin I, ng/mL	50.9 ± 90	128 ± 136	20 ± 28	<0.0001
+Peak creatinine phosphokinase, U/L	954 ± 1263	2017 ± 181	510 ± 492	<0.0001

* BMI ≥30kg/m^2 and/or waist circumference ≥88cm for women and ≥102cm for men

****** Comparison for STEMI vs. NSTEMI

^ 98 patients with angiographic results

+ Logarithm of peak troponin I and CPK was used to estimate p-values

Table 2A: Characteristics in obese vs. non-obese subjects with NSTEMI

Variable n = 73	*Obese n = 50	Non-Obese n = 23	p-value
Age, years	61.8 ± 12.8	67.1 ± 12	0.08
Sex, men	21 (42)	16 (70)	0.02
Race, %			
African-American	32 (64)	12 (52)	
Caucasian	9 (18)	6 (26)	0.25
Hispanic	8 (16)	2 (9)	
Other	1 (2)	3 (13)	
BMI, km/m^2	33.1 ± 6.4	24.3 ± 3.5	<0.0001
Waist circumference, cm	110 ± 15	85 ± 10	<0.0001
Epicardial Fat, mm	6.1 ± 2.2	5.9 ± 2.3	0.76
Pericardial Fat, mm	6.7 ± 3.0	6.3 ± 2.4	0.57
Epicardial + Pericardial Fat, mm	12.9 ± 4.7	12.3 ± 4.4	0.62
Hypertension, %	47 (96)	20 (87)	0.16
Diabetes, %	28 (57)	5 (22)	0.004
Dyslipidemia, %	41 (82)	20 (91)	0.31
Smoking, %	23 (47)	12 (52)	0.67
Family history of coronary disease, %	29 (58)	9 (39)	013
History of coronary artery disease, %	23 (46)	10 (43)	0.84
Congestive heart failure, %	4 (8)	5 (23)	0.08
Obstructive sleep apnea, %	34 (68)	3 (13)	<0.0001
Ejection fraction, %	46.8 ± 11	42.1 ± 14	0.20
Onset of chest pain to peak enzyme, hrs.	20.1 ± 16	15.3 ± 23	0.38
Triple vessel disease^, %	20 (43)	7 (30)	0.29
Creatinine, mg/dL	1.2 ± 0.4	1.2 ± 0.4	0.94
+Peak troponin I, ng/mL	23.6 ± 31	17.8 ± 37	0.04
+Peak creatinine phosphokinase, U/L	590 ± 549	334 ± 274	0.05

* BMI $\geq$30kg/m^2 and/or waist circumference $\geq$88cm for women and $\geq$102cm for men

^ 70 patients with angiographic results

+ Logarithm of peak troponin I and CPK was used to estimate p-values

Table 2B Characteristics in obese vs. non-obese subjects with STEMI

Variable n = 29	*Obese n = 20	Non-Obese n = 9	p-value
Age, years	59.3 ± 13	55.6 ± 9	0.41
Sex, men	12 (60)	7 (78)	0.35
Race, %			
African-American	13 (65)	5 (56)	
Caucasian	5 (25)	2 (22)	0.14
Hispanic	2 (10)	0 (0)	
Other	0 (0)	2 (22)	
BMI, km/m^2	32.6 ± 4.9	23.5 ± 3.2	<0.0001
Waist circumference, cm	109 ± 12	86 ± 9.7	<0.0001
Epicardial Fat, mm	7.1 ± 2.2	4.9 ± 1.9	0.01
Pericardial Fat, mm	8.6 ± 3	6.6 ± 3.1	0.12
Epicardial + Pericardial Fat, mm	15.8 ± 3.8	11.5 ± 4.7	0.03
Hypertension, %	19 (95)	8 (89)	0.54
Diabetes, %	7 (35)	3 (33)	0.93
Dyslipidemia, %	15 (75)	5 (26)	0.29
Smoking, %	6 (30)	6 (67)	0.06
Family history of coronary disease, %	11 (55)	3 (33)	0.28
History of coronary artery disease, %	2 (10)	2 (22)	0.37
Congestive heart failure, %	0 (0)	0 (0)	-
Obstructive sleep apnea, %	14 (70)	4 (44)	0.18
Ejection fraction, %	47 ± 11	39 ± 12	0.15
Onset of chest pain to peak enzyme, hrs.	12.4 ± 4.6	11.2 ± 4.8	0.55
Triple vessel disease^, %	3 (16)	3 (33)	0.29
Creatinine, mg/dL	1.3 ± 0.3	1.4 ± 0.7	0.62
+Peak troponin I, ng/mL	104 ± 141	182 ± 114	0.02
+Peak creatinine phosphokinase, U/L	1723 ± 1776	2636 ± 1848	0.17

* BMI $\geq$30kg/m^2 and/or waist circumference $\geq$88cm for women and $\geq$102cm for men

^ 28 patients with angiographic results

+ Logarithm of peak troponin I and CPK was used to estimate p-values

Table 3A Univariate predictors of peak troponin I and CPK levels in NSTEMI

Variable for peak troponin I	F-ratio	p-value
Hypertension	6.00	0.017
***Obesity**	4.59	0.035
Race	2.91	0.092

Variable for peak CPK	F-ratio	p-value
Hypertension	6.97	0.010
***Obesity**	4.13	0.046

* BMI $\geq$30kg/m^2 and/or waist circumference $\geq$88cm for women and $\geq$102cm for men

Table 3B Univariate predictors of peak troponin I and CPK levels in STEMI

Variable for peak troponin I	F-ratio	p-value
Epicardial + Pericardial Fat	-4.02	0.055
Age	3.92	0.057
***Obesity**	-3.66	0.066
Epicardial fat	-3.43	0.075

Variable for peak CPK	F-ratio	p-value
History of coronary artery disease	4.36	0.047
Epicardial + Pericardial Fat	-3.94	0.058
Diabetes	3.77	0.063
Age	3.47	0.074

* BMI $\geq$30kg/m^2 and/or waist circumference $\geq$88cm for women and $\geq$102cm for men

Table 4A Multivariate predictors of peak troponin I and CPK levels in NSTEMI

Variable for peak troponin I	F-ratio	p-value
***Obesity**	5.43	0.023
Hypertension	2.96	0.091

Variable for peak CPK	F-ratio	p-value
Hypertension	5.42	0.024
***Obesity**	5.38	0.024

* BMI $\geq$30kg/m^2 and/or waist circumference $\geq$88cm for women and $\geq$102cm for men

Table 4B Multivariate predictors of peak troponin I and CPK levels in STEMI

Variable for peak troponin I	F-ratio	p-value
***Obesity**	-4.47	0.054

Variable for peak CPK	F-ratio	p-value
Diabetes	3.48	0.086

* BMI $\geq$30kg/m^2 and/or waist circumference $\geq$88cm for women and $\geq$102cm for men

Multivariate analyses adjusted for: Age, sex, race, hypertension, diabetes, dyslipidemia, smoking, history of coronary disease, congestive heart failure, obstructive sleep apnea, triple vessel disease and time of onset of chest pain.

Table 5A Correlations between BMI, waist circumference, epicardial fat, pericardial fat and epicardial + pericardial fat with peak troponin I and CPK in patients with NSTEMI

	Peak Troponin I	Peak CPK
BMI	0.24, p=0.03	0.28, p=0.02
Waist circumference	0.12, p=NS	0.24, p=0.05
Epicardial Fat	0.08, p=NS	0.04. p=NS
Pericardial Fat	-0.06, p=NS	-0.07, p=NS
Epicardial and Pericardial Fat	0.01, p=NS	-0.03, p=NS

NS = p-value >0.10

Table 5B Correlations between BMI, waist circumference, epicardial fat, pericardial fat and epicardial + pericardial fat with peak troponin I and CPK in patients with STEMI

	Peak Troponin I	Peak CPK
BMI	-0.25, p=NS	-0.18, p=NS
Waist circumference	-0.05, p=NS	-0.02, p=NS
Epicardial Fat	-0.33, p=0.08	-0.31, p=0.10
Pericardial Fat	-0.29, p=NS	-0.34, p=0.06
Epicardial and Pericardial Fat	-0.34, p=0.07	-0.36, p=0.05

NS = p-value >0.10