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Marta Isabel Fontes de Oliveira

Epicardial and visceral fat are independent determinants of diastolic dysfunction after myocardial infarction

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TÍTULO DISSERTAÇÃO
Epicardial and visceral fat are independent determinants of diastolic dysfunction after myocardial infarction

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TITLE

Epicardial and visceral fat are independent determinants of diastolic dysfunction after myocardial infarction

SHORT TITLE

Adipose Tissue Distribution and Diastolic Function

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ABSTRACT:

Aims: Recent studies have associated obesity with subclinical diastolic dysfunction (DD). However, few data are available on the relative contribution of adiposity distribution on changes in myocardial structure and function. Our aim was to evaluate the role of abdominal fat distribution (visceral versus subcutaneous) and epicardial fat volume on diastolic function in patients after acute myocardial infarction (AMI).

Methods and Results: One month after AMI, 225 consecutive patients were prospectively enrolled and underwent detailed transthoracic echocardiography (mitral inflow analysis, pulmonary vein flow, tissue Doppler evaluation), computed tomography (quantification of epicardial fat volume and total, subcutaneous and visceral abdominal fat) and anthropometric evaluation with bioimpedance analysis.

We found a significant association between DD parameters, such as E' velocity, with body mass index ($r= -0.16; p=0.02$), fat mass percentage ($r= -0.25; p=0.02$) and waist perimeter ($r= -0.27; p<0.001$). E' velocity and E/E' ratio were significantly correlated with total and visceral abdominal fat area ($r=-0.27$, $p<0.001$ and $r=0.21$, $p<0.01$ respectively), but not with subcutaneous fat.

After multivariate regression analysis, epicardial adipose tissue (EAT) showed a significant association with lateral E' velocity ($p<0.01$) and increased E/E' mean ratio ($p<0.01$). Patients with diastolic dysfunction had higher EAT volumes (116.7±67.9 ml versus 93.0±52.3 ml; $p=0.01$) and there was a progressive increase in EAT according to increasing severity DD grades (p for trend =0.001).

None of the adiposity parameters correlated with systolic function parameters.

Conclusions: Obesity, mainly central and visceral fat, was significantly correlated with DD parameters. Increased epicardial fat volume was also an independently correlated with impaired diastolic function.

KEY WORDS:

Epicardial adipose tissue; Visceral adipose tissue; diastolic function

1. INTRODUCTION

Diastolic dysfunction (DD) is characterized by an abnormality of the left ventricle to relax and/or to fill with an adequate volume of blood, at normal diastolic filling pressures (1, 2). This disorder is common in the community (3) and is recognized as an important predictor of heart failure (4) and long-term mortality (3, 5). After acute myocardial infarction, the importance of diastolic function assessment has been frequently overlooked. However, in these patients DD is a major determinant of adverse clinical outcome (6) and decreased functional capacity. Left ventricle (LV) diastolic dysfunction is mainly associated with age, hypertension, coronary artery disease (CAD) and/or diabetes (7). Some very recent studies have also demonstrated that obesity is related with subclinical DD (8, 9). There are several pathophysiological pathways that can explain this association, involving both indirect and direct mechanisms (10). First, obesity is associated with several other comorbidities, such as hypertension, diabetes mellitus and CAD that can impact diastolic function (11). On the other hand, obesity can directly affect cardiac structure and function, causing chronic volume overload, hyperdynamic circulation and increased peripheral resistance, which induces increased LV preload and afterload (9, 12). Furthermore, it is also recognized that the adipose tissue, especially visceral fat, can induce a pro-inflammatory state and secrete several adipokines which can directly influence myocardial structure and function (13).

Only a few previous studies have assessed the relative importance of visceral versus subcutaneous adiposity as determinants of DD. The few data available suggest that visceral fat, the most metabolically active fat depot, can be a more important determinant of DD (14). Moreover, the heart itself is covered by fat, the epicardial adipose tissue (EAT) (15). Because EAT secretes proinflammatory, proatherogenic and protrombotic adypokines (16, 17) and there is no physical barrier separating it from the adjacent myocardium and coronary arteries, EAT can have a local metabolic role by a paracrine effect (18). In fact, several studies have demonstrated that EAT is associated with the development and progression coronary artery disease (19-23), independently of other cardiovascular risk factors or other fat deposits, and possibly with changes in myocardial structure and function (24-27).

In this study our aims were to assess: 1) the role of total versus central adiposity parameters as determinants of diastolic dysfunction; 2) the relative importance of total, subcutaneous and visceral abdominal fat mass in this association; 3) the influence of epicardial adipose tissue on myocardial systolic and diastolic function.

2. METHODS

2.1. Patient population and study protocol

The present study included 225 consecutive patients referred to a cardiac rehabilitation program, one month after an acute myocardial infarction. Exclusion criteria were age above 75 years, inability to exercise, severe valvular heart disease, moderate or severe chronic lung disease, atrial fibrillation or exercise induced myocardial ischaemia. All patients were prospectively enrolled and were submitted on the same day to clinical evaluation (performed by a cardiologist), anthropometric evaluation, detailed transthoracic echocardiography, computed tomography (CT) scan and blood sample collection.

The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by the institution's ethical committee. All patients gave their written informed consent.

2.2. Anthropometric evaluation

Measurements included height, weight and waist circumference (WC). Body mass index (BMI) was calculated for each subject. WC was measured at the midpoint between the iliac crest and the lower rib margins, measured in the midaxillary line. According to World Health Organization criteria, overweight was defined as body mass index (BMI) between 25 and 30 Kg/m^2 and obesity as BMI>30 kg/m^2. Abdominal obesity was defined as WC>102 cm in men and >88 cm in women.

Body composition assessment was performed by bioelectrical impedance analysis (Tanita Column Adult Weighing Scale®) to determine body fat percentage (%).

2.3. Echocardiography assessment protocol

All echocardiography studies were acquired by a single experienced cardiologist using an ultrasound system (iE33, Philips Medical Systems, Best, The Netherlands) equipped with a S5-1 transducer. Images were digitally stored for posterior offline analysis.

Cardiac chambers dimensions; volumes and left ventricular mass were measured according to current recommendations (28). Mitral inflow velocities were assessed using pulsed-wave (PW) Doppler in the apical four-chamber view, with a 3 mm sample placed between the tips of the mitral leaflets; velocities were recorded at end-expiration and averaged over three consecutive cardiac cycles. PW tissue-Doppler velocities were acquired at end

expiration, in the apical four-chamber view, with the sample positioned at the septal and lateral mitral annulus. PW Doppler velocities at the upper right pulmonary vein were also recorded. For all parameters the average of three consecutive heartbeats was recorded.

Diastolic function was assessed according to the recent consensus guidelines on diastolic function evaluation (29) by determining peak early (E) and late (A) diastolic mitral inflow velocities, deceleration time of early left ventricular filling (DT), the E/A ratio, the septal, lateral and average myocardial annular tissue velocity (E'sep, E'lat, E'mean, respectively), the E/E' ratio (also the septal, lateral and mean E/E'), pulmonary vein flow analysis (to calculate the Ard-Ad difference: the time difference between the duration of the atrial reversal wave of the pulmonary flow – Ard – and the mitral A-wave duration) and isovolumic relaxation time (IVRT). Using the recent EAE/ESC guidelines on diastolic function evaluation (29), patients were categorized in diastolic dysfunction (DD) grades – normal, grade I (mild DD), grade II (moderate DD) and grade III (severe DD), by two independent cardiologists who were blinded for the study data. In case of discordance, each case was discussed individually, and if doubt persisted no grade was endorsed, which happened in 20 patients (8.9%).

2.4. CT scan protocol: Abdominal and Epicardial Fat assessment

Multidetector CT scans were performed in all patients using a 64-slice CT scanner (Somatom Sensation 64, Siemens Medical Solutions, Forchheim, Germany) with two different acquisitions: one for abdominal fat quantification and the other for epicardial adipose tissue quantification.

To assess abdominal fat, a single-slice abdominal CT scan was performed between L4 and L5, according to the method described by Borkan et al (30). The scan parameters were 120 kV and 216 mAs with 5 mm thickness. This resulted in an estimated radiation exposure of 0.06 mSv. On the scan obtained, a cursor pointer was used to trace the abdominal visceral fat area, and the data were processed using a histogram-based statistical program according to the previously described method (31, 32). One expert, unaware of the patient's details, measured abdominal fat distribution. Fat tissue was defined in the range between -150 and -50 Hounsfield units (HU). Total abdominal fat area was measured and subcutaneous fat area was obtained by subtracting abdominal visceral fat from the total abdominal fat area.

An experienced radiographer, blinded for the purpose of the study and the patient's anthropometric data, quantified epicardial fat volume. A cursor pointer was used to manually trace the pericardial contour using 1-mm-

thick reconstructed axial slices. Pericardium contour was traced for every 10 mm, starting from the lower visible level of pulmonary artery bifurcation until the top level of the pulmonary valve, for every 20 mm from there until the first slice where the diaphragm becomes visible and, again, for every 10mm from this point until the last slice where pericardium is still visible (31), as illustrated in figure A.1. The pericardium contour was extrapolated by the software (Syngo Volume, Siemens Medical Solutions) for the non-traced slices and rechecked by the operator. Within these anatomical limits, EAT was identified using the adipose tissue attenuation references (from -150 to -50 HU) and a final EAT volume resulted from the sum of all slices of fat values.

2.5. Statistical analysis

Statistical analysis was performed with SPSS program version 20. All continuous variables are shown as a mean ± SD for normally distributed variables or as a median and interquartile range for non-normally distributed. Categorical variables are expressed as a number (n) and percentage (%). Statistical significance was defined as $p<0.05$.

Spearman correlation coefficient (r) was analysed to access the correlations between cardiac function and structure echocardiographic parameters and adiposity parameters obtained by anthropometry and CT scan. To compare median values of several adiposity parameters according to diastolic function grades, non-parametric tests were used (Mann–Whitney and Kruskal-Wallis, accordingly).

Linear regression analysis was performed for univariate and multivariate analysis of fat distribution variables that predict worse diastolic function. Multivariate analysis was performed accordingly with adjustment for age, hypertension, sex and several fat depots.

3. RESULTS

The clinical, anthropometric and analytical characteristics of the study population are summarized in table A.1. Most patients were men (84%), with a mean age of 55.1±10.9 years, 47.6% were overweight and 20.9% were obese. The mean ejection fraction was 53.6±9.3% and the majority of patients (64.4%)) had some degree of diastolic dysfunction: 27.8% had grade 1 DD, 28.3% had grade 2 DD, 4.4% had severe DD and 35.6% had normal diastolic function.

3.1. Diastolic function and adiposity parameters

As shown in table A.2, there was a significant correlation between BMI and decreased early diastolic velocity (E' lateral) and increased LV filling pressures (E/E' mean). Fat mass percentage, assessed by bioelectric impedance analysis, was also inversely correlated with E' septal velocity (r= -0.26, p<0.01), E' lateral velocity (r= -0.25; p<0.01) and E/E' mean ratio (r= 0.28; p<0.01). On the other hand, as shown in table A.4, there was a significant increase in fat mass percentage, according to the classification in diastolic dysfunction grades (p for trend < 0.01). After multivariate analysis, with adjustment for age, sex and hypertension history, the association between fat mass percentage and early diastolic velocities (E' septal and lateral) remained significant, as shown in table A.3. The correlation between diastolic function and adiposity parameters is better with central obesity (assessed by waist-perimeter/height) than with total fat parameters, such as BMI (table A.2). Also, the association between waist-perimeter/height and E' lateral velocity is independent of BMI or fat mass percentage (p<0.01). As shown in table A.3, after multivariate adjustment, for each unit increase in waist-perimeter/height there is a decrease of -0.09 (95%CI: -0.15 to -0.03; p<0.01) in E' lateral velocity (see table A.3).

3.2. Association between diastolic function and abdominal fat mass (total, subcutaneous and visceral fat)

When analysing the association between diastolic function and abdominal fat distribution assessed by CT scan, increased total abdominal fat mass significantly correlated with decreased E' velocities and increased E/E' ratios (as shown in table A.2 and in figure A.1). Patients with diastolic dysfunction have increased total abdominal fat mass, as shown in table A.4.

There was a significant correlation between E' lateral and E' septal velocities with visceral abdominal fat mass, but not with subcutaneous fat, as shown in table A.2: r= -0.27, p<0.01, between E' lateral and visceral fat mass *versus* r= -0.09, p=0.20, between E' lateral and subcutaneous fat (see also figure A.1). According to the classification in diastolic dysfunction grades, we saw an increase in visceral abdominal fat (p for trend = 0.01) but not in subcutaneous abdominal fat mass (p for trend = 0.13) with worse diastolic function.

3.3. Epicardial fat volume and diastolic dysfunction

Epicardial fat volume was significantly correlated with all echocardiographic diastolic dysfunction parameters, namely with reduced lateral and septal E' velocities and with higher septal, lateral and mean E/E' ratios (table A.2 and figure A.3). Also, across diastolic dysfunction grades there is a progressive increase in epicardial fat volume

(p for trend, 0.001), as shown in figure A.4. Patients with any degree of diastolic dysfunction have significantly higher epicardial fat volumes (116.7±67.9 ml in patients with DD versus 93.0±52.3 ml in patients with normal diastolic function). The association between epicardial fat volume and E' lateral velocity is independent of other adiposity parameters ($p<0.01$ after adjustment for total fat mass percentage, $p<0.01$ after adjustment for total abdominal fat and $p=0.03$ after adjustment for visceral fat).

After multivariate regression analysis with adjustment for age, sex and hypertension, increased epicardial fat is associated with a decreased lateral E' velocity ($p<0.01$), septal E' velocity ($p=0.02$) and an increased E/E' mean ratio ($p<0.01$), as shown in table A.3.

3.4. Association of adiposity parameters with other cardiac structural and functional changes

No significant association was found between total body fat parameters such as BMI, waist-perimeter/height and fat mass percentage with systolic function, namely with ejection fraction or with systolic mitral annulus velocities determined by tissue Doppler (S' septal and S' lateral). Also, neither abdominal fat mass (either total fat, subcutaneous or visceral fat) neither epicardial fat volume correlate with any systolic function parameter (figure A.3).

4. DISCUSSION

In this study, we analysed the association of several adiposity parameters with diastolic function and observed that: 1) overall, there is a significant association between increased total adiposity and impaired diastolic function; 2) this association seems to be stronger with central/visceral adiposity than with subcutaneous or total fat parameters; and 3) the association of epicardial fat volume with diastolic dysfunction is independent of other cardiovascular risk factors (namely ageing and hypertension), gender and other adiposity parameters. On the contrary, we did not find any association between increased adiposity and systolic function.

The current study is, to the best of our knowledge, the first analysing in detail this recently discovered association between several adiposity parameters, including epicardial fat, and diastolic dysfunction. Fat distribution was analysed with classical anthropometry parameters, but also using CT scan data for determination of total, visceral and subcutaneous abdominal fat mass and epicardial fat volume. CT scan is considered the best method to assess epicardial fat (33). On the other hand, diastolic function was assessed according to the most recent consensus

document for the evaluation of left ventricle diastolic function (29) which recommends the analysis of tissue Doppler derived parameters especially, early mitral annulus velocity (E' wave) that is a relatively preload-independent index of LV relaxation and the ratio between peak early diastolic mitral inflow velocity and myocardial velocity (E/E') that can be used to estimate LV filling pressures (29). As recommended, for the categorization in DD grades the integrated diagnostic algorithm was also used which includes the analysis of mitral inflow pattern, tissue Doppler velocities, pulmonary vein flow and left atrium volume(29).

4.1. The relation of diastolic dysfunction with total and central adiposity

Our results are in accordance with very recent studies that have shown an association between increased adiposity and diastolic dysfunction (8, 34). In a general population sample, Russo *et al.* (34) found an association between increased BMI and reduced early diastolic mitral annulus velocity (E'), increased filling pressures (E/E') and the presence of diastolic dysfunction. However, it is known that BMI is not a good marker of fat accumulation because it is influenced by several other factors (35). In our study, we have shown that worse diastolic function is associated not only with increased BMI, but also with increased fat mass percentage (assessed by bioelectric impedance), which reinforces the association between fat accumulation and diastolic dysfunction.

This association between obesity and diastolic function was independent of traditional cardiovascular risk factors, suggesting that other pathophysiological mechanisms are responsible for this association. Adipose tissue can modulate the cardiovascular system by several metabolic and neuroendocrine pathways, which include abnormalities in sodium balance, neuroendocrine activation of the renin-angiotensin-aldosterone axis and of the sympathetic system (36), secretion of adipokines that can directly influence myocardial structure and function (13), low grade-inflammation and increased myocardial oxidative stress (37).

It is also known that visceral adipose tissue is inherently different from subcutaneous fat in several processes involving lipolysis and lipogenesis. Visceral fat is the metabolically most active organ, secreting several adipokines and contributing to a systemic pro-inflammatory state that can affect cardiovascular system (13). On the other hand, inflammation has been linked with diastolic dysfunction in patients with hypertension (38) and coronary artery disease (39) and experimental studies have shown that inhibition of inflammatory pathways can prevent diastolic dysfunction (40). Integrating these recent data, Paulus *et al.* (41) proposed a novel paradigm for the development of heart failure with preserved ejection fraction which identifies a systemic pro-inflammatory

state (induced by obesity and other comorbidities) as a cause of reduced nitric oxide availability and decreased protein kinase G activity, therefore inducing stiffer cardiomyocytes and interstitial fibrosis deposition and, as a consequence, diastolic dysfunction.

In our study, diastolic dysfunction correlated more strongly with central and visceral adiposity parameters than with measures of total and subcutaneous obesity. A similar finding showing an association between waist-perimeter and diastolic dysfunction, independent of BMI, has also been recently demonstrated in the general population (8). Another study from the Baltimore Longitudinal Study of Aging, in which abdominal visceral and subcutaneous fat was measured using CT scan, also showed that although both visceral and subcutaneous fat were associated with LV diastolic dysfunction, only visceral fat was significantly associated with LV diastolic dysfunction when both were included in the same model (14). Our data are also in accordance with these findings.

4.2. The association between epicardial fat and diastolic function

In this study we have shown that increased epicardial fat volume was significantly associated with worse diastolic function. This association was independent of other diastolic dysfunction determinants, such as ageing, sex and hypertension history. A similar finding has been recently reported showing an association between epicardial fat thickness (determined by echocardiography), but not visceral adipose tissue, with subclinical diastolic in peritoneal dialysed patients (25).

Epicardial fat has special properties that distinguish it from other visceral fat components. It directly covers the heart and the coronary arteries without any mechanical barrier to the cardiomyocytes and vessels and also sharing the same blood supply (42). Therefore, because EAT is an important source of several pro-inflammatory and pro-atherogenic cytokines, EAT can have a direct effect on coronary atherosclerosis and/or cardiac structure and function (18, 43). Recently, several studies have recognized increased EAT as an independent determinant of the development and progression of coronary artery disease (CAD) (22, 31, 44), presence of myocardial perfusion abnormalities (45) and vulnerable coronary atherosclerotic plaques (21). EAT is a stronger determinant of CAD than visceral adiposity located in other body compartments (19).

EAT can also directly influence myocardial structure and function by mechanical, systemic and paracrine pathways. The systemic effects of obesity on cardiac function were described above. Our data are in accordance with other studies (25-27) suggesting a direct influence of EAT on diastolic function, possibly mediated by local

mechanical or paracrine effects. First, epicardial fat volume can range from 50 g to >250 g and, therefore, induce an outside compression of the heart which can pose a mechanical limitation to cardiac expansion, further deteriorating DD (24). Local paracrine inflammatory pathways can also play an important role in this association. In an interesting study, using biopsies of patients undergoing elective CABG, it was shown that epicardial adipose tissue is a local source of several inflammatory mediators (such as IL-1 beta, IL-6, MCP-1, and TNF-alpha) independent of plasma inflammatory biomarkers (16). As stated above, inflammation can induce stiffer cardiomyocytes, increased interstitial fibrosis deposition and diastolic dysfunction (41). Moreover, EAT can also secrete locally several adipokynes (such as adiponectin, resistin, leptin and others) (16, 46) that can induce changes in myocardial structure and function (42). Finally, EAT is a source of free fatty acids (FFA), leading to the accumulation of myocardial triglycerides, cardiomyocyte apoptosis, oxidative stress and impaired cardiac function(47, 48).

Epicardial fat has also been reported to correlate with structural changes of the heart such as left atrial enlargement (an indirect and chronic marker of diastolic dysfunction), increased LV end-diastolic volume and greater LV mass index (24, 26, 49). However, the amount of EAT doesn't appear to be directly related with cardiac systolic dysfunction. We found no significant correlation between EAT and any systolic function parameter, including ejection fraction or tissue Doppler derived S' septal and lateral velocities.

In summary, because epicardial adipose tissue correlates with the incidence and progression of CAD, with changes in myocardial structure and impaired diastolic function it has been proposed that measurement of epicardial fat (preferably by CT scan or, alternatively, by echocardiography) can possibly serve as an additional tool for cardiovascular risk stratification (42). Although further studies are needed before this can be recommended in clinical practice, in a registry of 2751 asymptomatic individuals it has been shown of that adding epicardial fat to standard coronary calcium score and Framingham risk score improves specificity and accuracy in predicting major adverse cardiovascular events (MACE) (50).

4.3. Study limitations

This study follows a cross-sectional design, and therefore it does not allow inferring about causality relation between adiposity parameters and diastolic dysfunction. Longitudinal studies are now required to further assess this association.

Also, we have only included patients after myocardial infarction, and therefore we cannot extrapolate these conclusions to the general population and other cardiac diseases.

4.4. Conclusions

In this population, impaired diastolic function is associated with increased adiposity parameters, especially with visceral and central fat parameters. The association between epicardial fat volume and diastolic dysfunction is independent of traditional cardiovascular risk factors and other adiposity parameters.

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Disclosures

None.

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LEGENDS

Figure A.1. Measurement of epicardial fat volume by computed tomography.

The level of the axial slices used for pericardial delineation is shown in a coronal projection. EAT was identified within the limits of pericardium sac using the adipose tissue attenuation references (-50 to -150 HU). Pericardium contour was traced for every 10 mm, starting from the lower visible level of pulmonary artery bifurcation until the top level of the pulmonary valve; for every 20 mm from there until the first slice where the diaphragm becomes visible; and for every 10mm from this point until the last slice where pericardium is still visible. Final EAT volume quantification was calculated as the sum of all slices fat values.

Figure A.2. Scatter plots showing the association between several adiposity parameters and diastolic function, assessed by E' lateral velocity

r: correlation coefficient between the two variables

Figure A.3. Distribution of epicardial fat volume according to diastolic dysfunction grades.

* $p<0.05$ compared to patients with normal diastolic function;

† $p<0.01$ compared to patients with normal diastolic function

Clinical Data	
Age, years	55,1 ± 10.9
Male	189 (84.0%)
Cardiovascular Risk Factors	
Hypertension	35 (15.6%)
Type 2 Diabetes	35 (15.6%)
Dyslipidemia	119 (52.9%)
Smoker	117 (52.0%)
Familial History	22 (9.8%)
AMI	
ST-segment elevation	85 (37,8%)
Non ST-segment elevation	140 (62.2%)
PCI	191 (84.9%)
Anthropometry and Fat distribution	
Overweight , WHO	107 (47.6%)
Obese, WHO	47 (20.9%)
BMI, Kg/m^2	26.9 ± 4.5
Weight, kg	76.0 ± 12.9
Waist perimeter, cm	96.8 ± 10.0
Bioimpedance fat mass, %	26.0 ± 7.3
Total abdominal fat, cm^2	343.1 ± 163.8
Subcutaneous fat, cm^2	182.5 ± 82.6
Visceral fat, cm^2	148.7 ± 70.5
Epicardial fat, cm^3	113.6 ± 43.2

Analytical Data	
Total cholesterol, mg/dL	137.5 ± 32.3
HDL, mg/dL	39.9 ± 10.3
LDL, mg/dL	75.4 ± 35.5
Triglycerides, mg/dL	123.3 ± 56.7
Glucose, mg/dL	97.1 ± 18.8
Hemoglobin, g/L	14.1 ± 1.4
A1c hemoglobin, %	5.9 ± 0.9
NTProBNP	357.0 ± 531.0
High sens. C-reative protein, mg/dL	0.35 ± 0.70
Echocardiography	
Septum, mm	9.6 ± 1.6
Posterior wall, mm	9.3 ± 1.5
LV mass index, g/m2	105.3 ± 25.0
RWT, unit	0.35 ± 0.07
Left atrium volume index, ml/m^2	34.8 ± 9.3
LV end-diastolic volume, ml/m^2	111.3 ± 30.6
LV end-systolic volume, ml/m^2	52.4 ± 22.4
LVEF, %	53.6 ± 9.3
E wave velocity, cm/s	78.1 ± 19.4
A wave velocity, cm/s	68.1 ± 17.6
E/A	1.22 ± 0.50
Deceleration time, ms	221.8 ± 49.8
IVRT, ms	98.7 ± 24.4
E' lateral velocity, cm/s	9.8 ± 2.3
E' septal velocity, cm/s	6.9 ± 1.8
E/E' (mean) ratio	10.4 ± 3.9
Diastolic dysfunction (DD) grade	
Normal	80 (39.0%)
Grade 1: mild DD	57 (27.8%)
Grade 2: moderate DD	58 (28.3%)
Grade 3: severe DD	10 (4.9%)

Table 1 – Characterization of the study population

Data are expressed as mean ± standard deviation or number (percentage). AMI, acute myocardium inflation; PCI, percutaneous Coronary Intervention; WHO, World Health Organization; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NTProBNP, N-terminal pro-brain natriuretic peptide; LV, left ventricle; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; E, transmitral flow velocity during early ventricular filling; A, transmitral flow velocity during atrial contraction; E' lateral, tissue Doppler velocity at the lateral wall of the mitral annulus level during early ventricular filling; E' septal, Tissue Doppler velocity at the septal wall of the mitral annulus level during early ventricular filling.

	E' septal	E' lateral	E/E' lateral	E/E'septal	E/E' mean
BMI	-0.11 (p=0.11)	-0.16 (p=0.02)	0.21 (p=0.001)	0.18 (p=0.01)	0.18 (p<0.01)
Fat mass percentage	-0.26 (p<0.001)	-0.25 (p<0.001)	0.29 (p<0.001)	0.31 (p<0.001)	0.28 (p<0.001)
Waist perimeter/height	-0.27 (p<0.001)	-0.27 (p<0.001)	0.28 (p<0.001)	0.30 (p<0.001)	0.28 (p<0.001)
Total abdominal fat	-0.19 (p<0.01)	-0.20 (p<0.01)	0.26 (p<0.001)	0.23 (p=0.001)	0.22 (p<0.01)
Subcutaneous abdominal fat	-0.10 (p=0.15)	-0.09 (p=0.20)	0.20 (p<0.01)	0.20 (p<0.01)	0.17 (p=0.02)
Visceral abdominal fat	-0.23 (p=0.001)	-0.27 (p<0.001)	0.25 (p<0.001)	0.21 (p<0.01)	0.21 (p<0.01)
Epicardial fat	-0.26 (p<0.001)	-0.28 (p<0.001)	0.28 (p<0.001)	0.24 (p<0.001)	0.25 (p<0.001)

Table 2 - Correlation coefficients between several adiposity parameters and diastolic function.

Table 3 – Univariate and multivariate linear regression analyses for the association of diastolic function parameters (E' velocity and E/E' ratio) with adiposity parameters.

*Adjusted for age, hypertension history, sex.

β, regression coefficient. 95%CI, 95% confidence interval

	E' septal velocity			E' lateral velocity			E/E' ratio		
	Crude β (95% CI)	**Adjusted β* (95% CI*)**	**p value***	**Crude β (95% CI)**	**Adjusted β* (95% CI*)**	**p value***	**Crude β (95% CI)**	**Adjusted β* (95% CI*)**	**p value***
BMI	-0.05 (-0.10 to 0.00)	-0.05 (-0.09 to -0.01)	0.02	-0.08 (-0.16 to -0,01)	-0.09 (-0.16 to -0,02)	<0.01	0.09 (-0,03 to 0.20)	0.10 (-0.01 to 0.22)	0.08
Fat mass %	-0.06 (-0.09 to -0.03)	-0.04 (-0.07 to 0.00)	0.04	-0.09 (-0.14 to -0.04)	-0.08 (-0.13 to -0.02)	<0.01	0.09 (0.01 to 0.16)	0.08 (-0.02 to 0.17)	0.11
WP/height	-0.09 (-0.13 to -0.05)	-0.05 (-0.09 to -0.01)	0.02	-0,13 (-0.19 to -0.07)	-0,09 (-0.15 to -0.03)	<0.01	0.11 (0.02 to 0.21)	0.09 (-0.01 to 0.19)	0.07
Total abdominal Fat (x10)	-0.03 (-0.05 to -0.01)	0.02 (-0.04 to 0.00)	0.07	-0.05 (-0.07 to -0.02)	-0.03 (-0.06 to 0.00)	0.03	0.04 (0.00 to 0.09)	0.04 (-0.01 to 0.08)	0.09
Subcutaneous abdominal fat (x10)	-0.02 (-0.05 to 0.01)	-0.02 (-0.05 to 0.00)	0.23	-0.03 (-0,08 to 0.01)	-0.04 (-0.08 to 0.00)	0.07	0.04 (-0.03 to 0.11)	0.04 (-0.03 to 0.11)	0.25
Visceral abdominal fat (x10)	-0.06 (-0.09 to -0.03)	-0.03 (-0.06 to 0.01)	0.15	-0.10 (-0.15 to -0.05)	-0.05 (-0.10 to 0.00)	0.04	0.08 (0.001to 0.16)	0.08 (0.00 to 0.16)	0.06
Epicardial fat (x10)	-0.11 (-0.17 to -0.06)	-0.06 (-0.12 to -0.01)	0.02	-0.17 (-0.25 to -0.09)	-0.11 (-0.19 to -0.03)	<0.01	0.19 (0.07 to 0.31)	0.19 (0.06 to 0.32)	<0.01

	Normal Diastolic function (n=80)	Grade 1 DD (n= 57)	Grade 2 DD (n= 58)	Grade 3 DD (n= 10)	p value (for trend)
BMI	25.8 ± 4.23	26.9 ± 5.6	26.8 ± 3.7*	25.7 ± 10.9	0.17
Fat mass %	22.1 ± 7.9	25.5 ± 11.7†	25.9 ± 9.2†	24.8 ± 16.1	<0.01
Waist perimeter/height	55.4 ± 7.0	58.3.0 ± 7.1†	58.5 ± 7.9†	56.2 ± 15.4	<0.01
Total abdominal fat	270.0 ± 151.6	331.1 ± 149.3*	321.0 ± 170.5†	308.8 ±300.6	0.02
Subcutaneous abdominal fat	155.32 ± 90.5	165.4 ± 99.6	175.3 ±74.7	194.4 ± 135.9	0.13
Visceral abdominal fat	111.6 ± 103.7	141.0 ± 75.9†	160.0 ± 88.8†	134.0 ± 155.6	0.01
Epicardial fat	93.0 ± 52.3	111.15 ± 60.2*	117.15 ± 64.3†	136.4 ± 83.1†	0.001

Table 4 – Distribution of adiposity parameters according to diastolic function grades.

Data expressed as median ± interquartile range;

* p<0.05 compared to patients with normal diastolic function;

† p<0.01 compared to patients with normal diastolic function

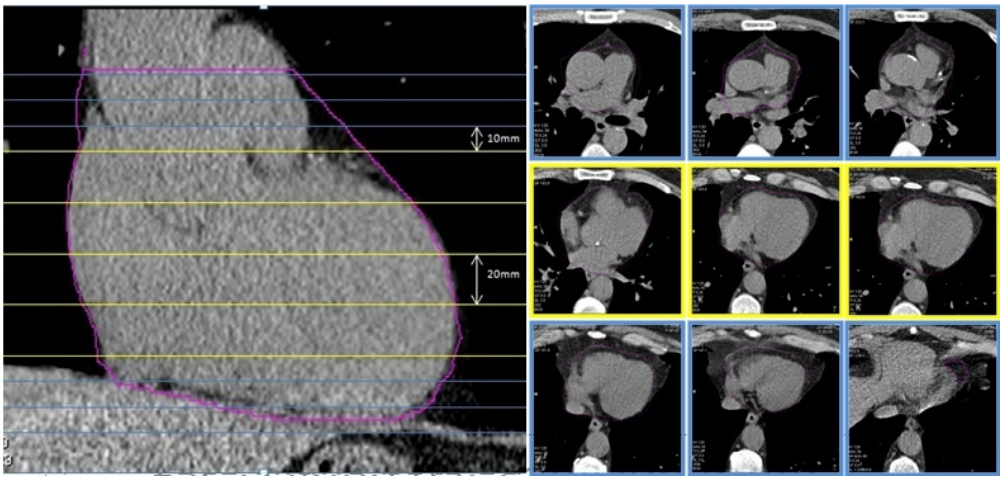

Figure A.1. Measurement of epicardial fat volume by computed tomography.

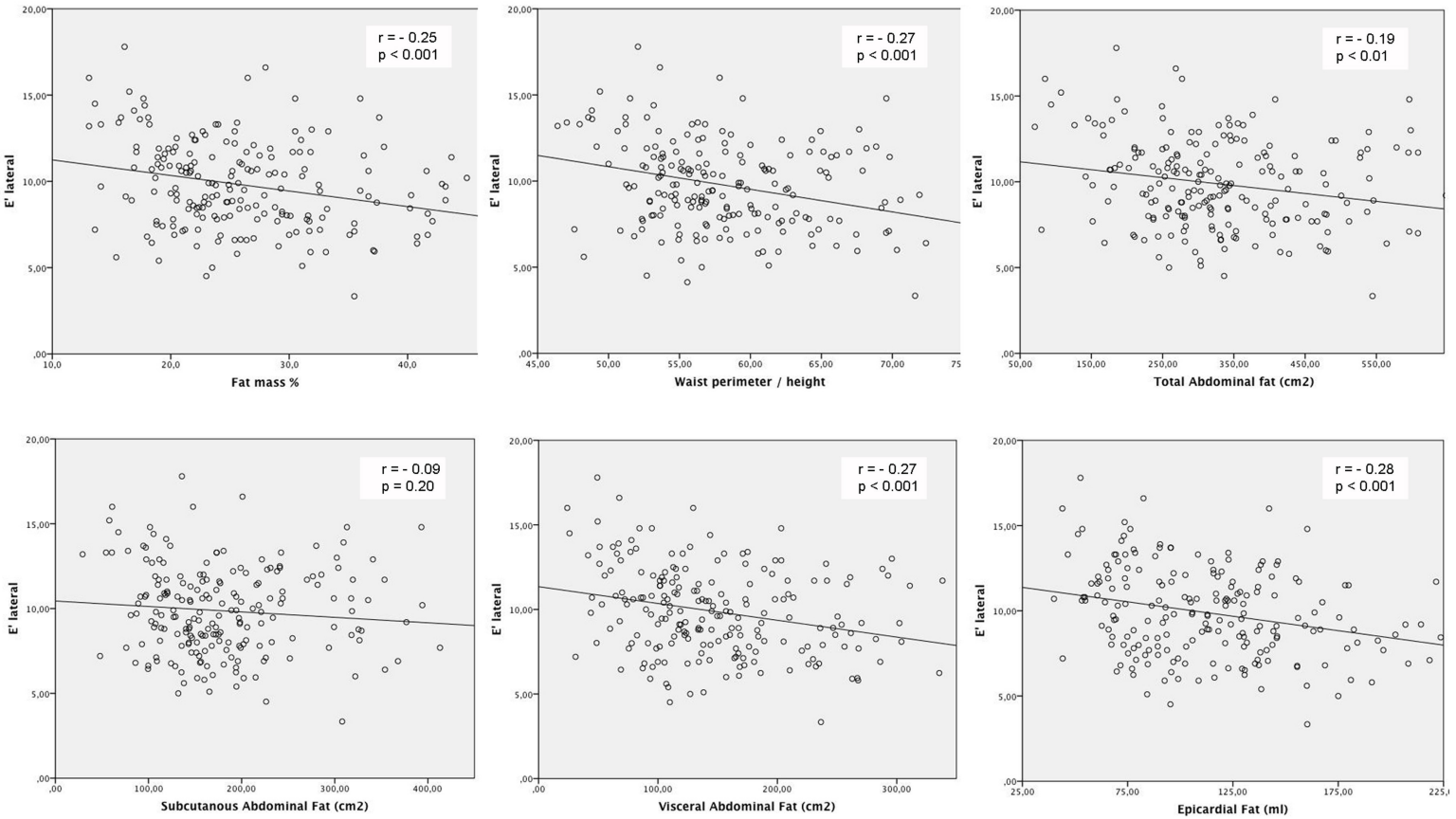

Figure A.2. Scatter plots showing the association between several adiposity parameters and diastolic function, assessed by E' lateral velocity

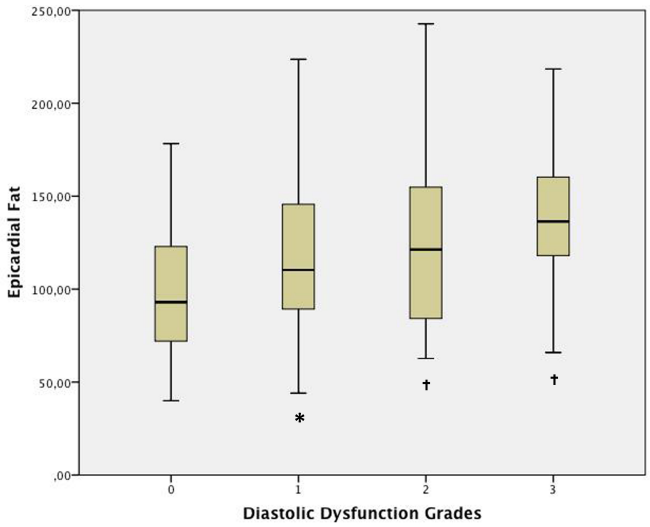

Figure A.3. Distribution of epicardial fat volume according to diastolic dysfunction grades.

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Anexos

European Journal of Heart Failure

INSTRUCTIONS TO AUTHORS

Scope of the Journal

The *European Journal of Heart Failure* is the International Journal of the European Society of Cardiology dedicated to the advancement of knowledge in the field of heart failure. The Journal publishes reviews and editorials in order to improve the understanding, prevention, investigation and treatment of heart failure. Molecular and cellular biology, pathology, physiology, electrophysiology, pharmacology, as well as the clinical, social and population sciences all form part of the discipline that is heart failure. Accordingly, submission of manuscripts on basic, clinical and population sciences is invited. Original contributions on nursing, care of the elderly, primary care, health economics and other specialist fields related to heart failure are also welcome.

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The European Journal of Heart Failure participates in the HEART network which is a network of Editors from most cardiovascular journals. Information is exchanged between editors on a regular basis. The network has recently approved a common ethics standard.

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TRABALHO DE INVESTIGAÇÃO

159/2013

"Gordura Epicardica e os seus efeitos em doentes pós-enfarte"

Autorizado.

Dr. Jorge F. Santos
Diretor Clínico
29-8-2013

INSTITUIÇÃO: Faculdade Medicina Universidade Porto

INVESTIGADOR PRINCIPAL: Marta Isabel Fontes Oliveira

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Marta Isabel Fontes de Oliveira
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À Comissão de Ética do
Centro Hospitalar de Vila Nova de Gaia/Espinho

C.H.G.44497 08-AUG'13

Exma. Comissão,

Eu, Marta Isabel Fontes de Oliveira, aluna do actual 5º ano da Faculdade de Medicina da Universidade do Porto, venho por este meio requerer a vossa autorização para a análise de dados clínicos a integrar no âmbito da minha tese de mestrado, sobre o tema *Gordura Epicárdica e os seus efeitos em doentes pós-enfarte*, sob orientação do Dr. Ricardo Fontes de Carvalho.

O tecido adiposo epicárdico tem sido associado à doença cardiovascular ao longo dos últimos anos, constituindo um factor de risco independente de aterosclerose e eventos coronários. Com o estudo em causa proponho-me a estudar se o aumento do volume da gordura epicárdica se associa a uma deterioração da função cardíaca (sistólica e diastólica) em doentes pós enfarte, e se esta associação é independente de outros factores de risco cardiovascular, nomeadamente do volume de gordura visceral intraabdominal.

Para tal serão recolhidos retrospectivamente os dados previamente adquiridos do volume de gordura epicárdica, determinada por AngioTC, comparando com os vários parâmetros de avaliação da função ventricular esquerda, avaliados por ecocardiografia. O estudo será realizado através da análise de uma amostra de doentes previamente internados no Serviço de Cardiologia do Centro Hospitalar de Vila Nova de Gaia/Espinho por enfarte agudo do miocárdio.

Será assegurado anonimato e a confidencialidade total dos dados recolhidos.

Sem outro assunto, e na expectativa de vossas prezadas notícias, subscrevo-me deixando o meu contacto para eventuais dúvidas ou esclarecimentos que considerem necessários:

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Marta Isabel Fontes de Oliveira
marta.fontes.oliveira@gmail.com

Vila Nova de Gaia, 10 de Julho de 2013.

Marta Fontes Oliveira

(A aluna: Marta Oliveira)

(O orientador: Dr. Ricardo Fontes de Carvalho)

(O Director de Serviço de Cardiologia, Dr. Vasco Gama Ribeiro)

Parecer favorável.

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