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Pericardial fat, insulin resistance, and left ventricular structure and function in morbid obesity

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Abstract *Background and aim:* Morbid obesity is often accompanied by insulin resistance and increased ectopic fat surrounding the heart. We evaluated the relation of epicardial and pericardial fat with insulin resistance and left ventricular (LV) structure and function.
Methods and results: Epicardial and pericardial fat thicknesses were determined at 2-dimensional echocardiography in 80 morbid obese subjects [age 42 ± 12 years, 31% men, body mass index (BMI) 44.4 ± 7 kg/m^2]. LV hypertrophy (LV mass ≥51 g/m$^{2.7}$), inappropriately high LV mass for a given cardiac workload (observed vs predicted LV mass >128%), and stress-adjusted LV mid-wall fractional shortening were determined. Pericardial and epicardial fat thicknesses had direct associations with BMI ($r = 0.40$ and 0.45, both $p < 0.01$) and waist circumference ($r = 0.37$ and 0.45, both $p < 0.01$). Pericardial (partial $r = 0.35$, $p < 0.01$), but not epicardial fat thickness (partial $r = 0.05$, $p =$ n.s.), was correlated with homeostasis model assessment-insulin resistance after adjustment for BMI. Pericardial fat also had a strong negative correlation with mid-wall fractional shortening ($p = 0.01$) and a positive one with inappropriately high LV mass ($p < 0.01$), while no such relation was found for epicardial fat (both $p =$ n.s.). Independently of age, male sex, BMI, and anti-hypertensive treatment, pericardial fat thickness had an independent positive association with inappropriately high LV mass ($\beta = 0.29$, $p = 0.02$), and a negative one with stress-adjusted mid-wall fractional shortening ($\beta = -0.26$, $p = 0.04$).
Conclusions: Pericardial fat thickness is associated with insulin resistance, inappropriately high LV mass, and LV systolic dysfunction in obese individuals. Findings from this study confirm the existence of a connection between insulin resistance, cardiac ectopic fat deposition and cardiac dysfunction in morbid obesity.

The prevalence of obesity nearly tripled over the last 25 years in the Western countries [1], and the rise was even greater for morbid obesity [2]. Individuals with morbid obesity are highly prone to develop insulin resistance, dyslipidemia, hypertension, metabolic syndrome, diabetes and other conditions linked with excess cardiovascular (CV) mortality [3].

In addition to the total amount of fat mass, body fat distribution plays a key role in modulating the link between obesity and CV risk. Measures of abdominal obesity reflecting increased visceral fat, such as waist circumference or waist-to-hip ratio, carry an increased risk of CV

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death independently of body mass index (BMI) [4,5]. Ectopic adiposity, defined as the amount of fat stored into non-adipose ectopic tissues, such as the liver, heart or muscles [6], has been proposed as a tool for distinguishing individuals at increased risk of developing metabolic disturbances and clinically overt CV disease. At any given BMI level, subjects with ectopic fat excess are more likely to develop hyperinsulinemia, insulin resistance, hypertension, metabolic syndrome and diabetes, all features strongly related to atherosclerosis and increased CV risk [7].

The adipose tissue surrounding the heart, namely pericardial and epicardial fat, is a marker of total ectopic fat deposits, and has been postulated to be involved in the pathophysiology of cardiac structural and functional changes through systemic and local toxic effects [8,9]. Population-based studies confirmed the relationship of cardiac adiposity with impaired coronary flow reserve [10] and incident coronary heart disease [11]. Pericardial and epicardial fat volumes are reliably quantified through computerized tomography or magnetic resonance imaging, although large-scale use of those techniques is limited by cost considerations, availability, use of ionizing radiations and, in some cases, restrictions due to the physical footprint in extremely obese individuals. The measurement of pericardial and epicardial fat thickness on 2-dimensional echocardiography at the free wall of the right ventricle in parasternal long-axis view has been proposed as an easier way to routinely evaluate the degree of cardiac adiposity [12]. In obese subjects, epicardial fat thickness was found to be related to left ventricular (LV) mass [13], insulin resistance [14] and features of metabolic syndrome [15].

Although specific anatomic, embryologic and functional features of pericardial and epicardial adipose deposits have been recognized, no studies have hitherto specifically compared the different relationships of pericardial and epicardial fat thickness with the metabolic profile and with cardiac structure and function. We undertook the present study with the aim of evaluating the link of epicardial and pericardial thickness at echocardiography with markers of insulin resistance and indexes of LV structure and function in morbid obesity.

Methods

Subjects

From November 2010 to December 2012 a total of 121 consecutive patients with morbid obesity (mean age 43 ± 13 years, 35% men, 43.9 ± 7 kg/m^2) were referred to the Unit of Internal Medicine, Angiology and Atherosclerosis of Perugia University for a comprehensive cardiovascular and metabolic assessment. All of them were potential candidates for bariatric surgery according to the National Institutes of Health Consensus Development criteria [16].

We excluded from the study patients with known cardiovascular disease (n = 15; heart failure, coronary artery disease, cerebrovascular disease, peripheral artery disease, atrial fibrillation), secondary forms of hypertension (n = 1), chronic kidney disease (n = 5), diabetes mellitus (n = 11), or other significant diseases (n = 4). A total of 5 patients were excluded because of low-quality echocardiographic images. The resulting study population consisted of 80 subjects (mean age 42 ± 12 years, 31% men).

All patients underwent a careful clinical examination. BMI was defined as weight (Kg)/squared height (m^2). Waist circumference was measured at the level of the upper border of the iliac crest with a measuring tape, at the end of a normal expiration. Blood pressure was obtained in triplicate by a physician, with a mercury sphygmomanometer and a brachial cuff placed around the non-dominant arm. Cuffs of appropriate size were chosen.

After an overnight fasting, blood was drawn and the following parameters determined: total cholesterol, triglycerides (enzymatic colorimetric method), high-density lipoprotein cholesterol (enzymatic colorimetric method after precipitation with polyethylenglycole), glucose (automated analyzer), glycated hemoglobin (high pressure liquid chromatography). Serum insulin was determined by a highly specific radioimmunoassay method (Linco Research, Inc). A homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from the model described by Matthews et al. [17] by means of the following equation: HOMA-IR = fasting serum insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5. A value of HOMA-IR ≥2.6 was adopted as the cut-off level for the diagnosis of insulin resistance [18]. Hypertension was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or current use of BP-lowering drugs. Type II diabetes mellitus was defined as serum fasting glucose ≥126 mg/dL, glycated hemoglobin ≥6.5%, or current use of antidiabetic drugs, according to World Health Organization criteria [19]. The study was conducted in accordance with the declarations of Helsinki and Tokyo. Favorable ethical approval for the study was obtained, and written informed consent was provided from all subjects.

LV structure and function

The echocardiographic study was performed with a commercially available device (MyLab 60, Esaote, Genoa, Italy).

The M-mode echocardiographic study of the left ventricle was performed under 2-dimensional control according to the American Society of Echocardiography recommendations [20] by 2 investigators (GP, GS) who were unaware of patients' clinical data. When optimal M-mode visualization was not obtained (n = 13 subjects), values were acquired using the parasternal long-axis 2-dimensional approach. LV mass was normalized by height$^{2.7}$ to correct for the effect of overweight, and LV hypertrophy was defined as an LV mass index ≥51 g/m$^{2.7}$ [21]. LV relative wall thickness was calculated as 2 × (posterior wall thickness)/LV internal diameter, and concentric geometry was defined by a relative wall thickness ≥0.43. The percentage of LV mass exceeding that predicted on the basis of cardiac workload was individually calculated as the ratio between observed/predicted LV