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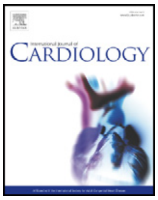

Association of epicardial fat thickness with the severity of obstructive sleep apnea in obese patients[☆]

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ABSTRACT

Background: The correlation between obesity and severity of obstructive sleep apnea (OSA) is controversial. Although fat excess is a predisposing factor for the development of OSA, it has not been determined whether fat distribution rather than obesity *per se* is associated with OSA severity. Epicardial fat thickness (EFT) is an independent index of visceral adiposity and cardiometabolic risk. We investigated the relation between fat distribution and cardiometabolic risk factors, including EFT and common carotid intima-media thickness (cIMT), with the severity of OSA in obese patients.

Methods: One hundred and fifteen obese patients (56 males, 59 females) with polysomnographic evidence of OSA (≥5 apnea/hypopnea events per hour) of various degrees, without significant differences in grade of obesity as defined by body mass index (BMI), were evaluated. The following parameters were measured: BMI, body composition by dual energy X-ray absorptiometry, EFT, right ventricular end-diastolic diameter (RVEDD) and cIMT by ultrasound, and parameters of metabolic syndrome (waist circumference, arterial blood pressure, fasting glucose, HDL-cholesterol and triglycerides).

Results: EFT, RVEDD, cIMT and trunk/leg fat mass ratio showed a positive correlation with OSA severity in univariate analysis ($r = 0.536$, $p < 0.001$; $r = 0.480$, $p < 0.001$; $r = 0.345$, $p < 0.001$; $r = 0.330$, $p < 0.001$, respectively). However, multiple linear regression analysis showed that EFT was the most significant independent correlate of the severity of OSA ($R^2 = 0.376$, $p = 0.022$).

Conclusions: The present study suggests that, in obese patients, EFT may be included among the clinical parameters associating with OSA severity. The association of EFT with OSA, both cardiovascular risk factors, is independent of obesity as defined by classical measures.

1. Introduction

Epicardial fat is the visceral fat depot of the heart [1] and reflects visceral adiposity rather than general obesity. It is considered a metabolically active tissue, being a local source of pro-inflammatory factors associated with the development of metabolic syndrome and cardiovascular diseases. Obstructive sleep apnea (OSA) is a sleep disorder characterized by repeated partial or complete collapse of the upper airways, which leads to oxygen desaturation, fragmentation of sleep, and daytime sleepiness, with associated features including cardiovascular and metabolic consequences [2–4]. Obesity, a major cause of morbidity and mortality through the development of its co-morbidities, is a predisposing factor in the development of OSA [5]. It is well established that the prevalence of OSA is higher among obese patients than in general population, and it is under diagnosed in overweight individuals [5]. OSA worsens with weight gain and improves with weight reduction [6] and may itself predispose to worsening obesity because of sleep deprivation and disrupted metabolism [7,8].

There are complex associations between OSA, clinical and subclinical cardiovascular and metabolic disorders and obesity, and early cardiovascular abnormalities in newly diagnosed OSA patients are observed [9]. Studies on the relationship between body mass index (BMI) and the severity of OSA are contradictory [10–13], and the question remains whether in obese individuals regional fat distribution more than BMI correlates with the severity of OSA.

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The aim of this study was to investigate, in an homogeneous population of obese patients, the association of OSA severity with markers of cardiometabolic disease risk and with estimated regional fat mass (FM), measured through traditional anthropometric measures, body composition and epicardial fat thickness (EFT).

2. Methods and procedures

2.1. Study population

We studied 115 obese patients with diagnosis of OSA (56 men and 59 women) recruited from the Department of Otolaryngology, Audiology and Phonation, Sapienza University of Rome from June 2010 to June 2011. Exclusion criteria comprised hypothyroidism, acromegaly, acute illness, current use of hypnotics, heart diseases, lung diseases, any other respiratory disorder, uncontrolled hypertension, craniofacial abnormalities, history of smoking, or use of continuous positive airway pressure (CPAP). Patients with a previous diagnosis of diabetes mellitus, dyslipidemia, or hypertension, were receiving drugs for each of these conditions. Metformin was used as glucose-lowering drug, fenofibrate as lipid-lowering treatment, and diuretics or sartans as blood pressure (BP)-lowering agents. Patients receiving other medications were excluded. All subjects were enrolled after written consent and approval by the Institution Ethic Committee.

2.2. Clinical measurements

Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. BMI was expressed as weight (kilograms)/height (m^2). Obesity was defined for any BMI ≥30 kg/m^2. The waist circumference (WC) was measured just above the bony landmark of the iliac crest and expressed in centimeters. Sitting BP was measured twice at 5-min intervals, and the average of two measurements was used for analysis.

2.3. Dual energy X-ray absorptiometry (DXA)

DXA analysis was performed by one single experienced technician using a DXA scan (Hologic Inc., Bedford, MA, USA, QDR 4500W). Coefficient of variation for fat mass was <1.5%. Body composition was measured in the whole body and in specific body regions. Delimiters for regional analysis were determined by a standard software (Hologic Inc., S/N 47168 VER. 11.2). With the use of specific anatomic landmarks, regions of the neck, trunk, arms and legs were distinguished. Scans were performed according to the manufacturer's instructions.

2.4. Polysomnography

In-hospital polysomnography (Somnoscreen^{TM} PSG, Somnomedix GmbH Nonnengarten, 8 D-97270 Kist, Germany) was performed overnight between 10:00 pm and 6:00 am in the same laboratory. Recordings included electroencephalogram, electrooculogram, electromyogram, electrocardiogram, thermistors for nasal and oral airflow, thoracic and abdominal impedance belts for respiratory effort, pulse oximetry for oxyhemoglobin level, tracheal microphone for snoring and sensor to assess changing of the position during sleep. Polysomnography records were scored according to standard criteria [14] by a single experienced operator. OSA degree was determined by the apnea/hypopnea index (AHI) defined as the total number of obstructive apneas (cessation of airflow for at least 10 s) and hypopneas (decrease of the airflow signal amplitude by at least 50% associated by oxyhemoglobin desaturation of at least 4% or by an arousal) per hour of sleep. Mild, moderate and severe OSA were defined by an AHI of 5–14, 15–29, and ≥30 events/h, respectively.

2.5. EFT, right ventricular end-diastolic diameter (RVEDD) and carotid intima-media thickness (cIMT) measurements

EFT was measured through a validated echocardiographic procedure [15]. Participants underwent high-resolution M-B-mode transthoracic echocardiography using a 2.5-MHz probe, and spectral Doppler exam of the common carotid artery using a 7.5-MHz probe (Esaote MyLab40, Esaote Europe B.V., The Netherlands). The EFT was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, and its thickness was measured perpendicularly on the free wall of the right ventricle (RV) at end-systole in three cardiac cycles. The average value of three cardiac cycles from each echocardiographic view was considered. The RVEDD was measured according to the recommendations of the American Society of Echocardiography. The cIMT was measured in the anterior wall of the common carotid artery as the distance from the trailing edge of the adventitia to the leading edge of the intima-media; in the posterior wall of the vessel, it was measured as the distance from the leading edge of the intima-media to the trailing edge of the adventitia. The cIMT values for any given subject were the mean value for the two common carotid arteries. All echocardiograms and carotid ultrasonography were recorded by the same experienced operator who was blinded to the other study data.

2.6. Laboratory

Blood samples were collected in the morning after an overnight fast. HDL cholesterol (HDL-C) and triglyceride concentrations were measured on fresh serum by an automated enzymatic method (Dimension Analyzer, Dade Behring S.p.A. Milano, Italy). All samples were assayed in duplicate with intraassay and interassay mean coefficients of variation of 2% and 4%, respectively. Fasting plasma glucose (FPG) determinations were performed using the hexokinase method (Aeroset, Abbott Park, IL, USA).

2.7. Statistical analysis

Data were analyzed with the use of STATISTICA software, version 6.1 (Stat Soft, Inc., Tulsa, Oklahoma). Results are expressed as mean ± SD. Differences between groups were analyzed using ANOVA for continuous variables. Pearson correlation test was used to measure a linear association between variables. The roles of sex, age, BMI, body fat distribution, cIMT, EFT, RVEDD, glucose and serum lipids as associated variables with AHI were tested by linear regression with the use of univariate and multivariate models. All p values presented are two-tailed, and values less than 0.05 are considered to indicate statistical significance.

3. Results

The demographic, anthropometric, clinical and sleep characteristics of the patients, as well as the comparisons of patients stratified according to AHI categories are shown in Table 1. Mean patient age was 53.64 ± 9.49 yr (range 30–65 yr), 48.7% of the participants were male and 51.3% were female. Their BMI was ≥30.0 kg/m^2 (mean, 36.30 ± 4.57 kg/m^2) with a mean value of 37.14 ± 4.76 kg/m^2 in females and 35.41 ± 4.22 kg/m^2 in males. The WC was constantly > 90 cm in females (mean, 109.49 ± 12.97 cm) and > 100 cm in males (mean, 111.78 ± 12.96 cm). Fifty patients (43.48%) presented with mild OSA. Moderate OSA was observed in 33 patients (28.70%), and severe OSA was found in 32 patients (27.82%). Although the women had a lower AHI than men (18.80 ± 17.55 *vs.* 29.70 ± 20.67, respectively; $p = 0.002$) the differences between categories of OSA severity were not statistically significant for confounding caused by gender ($p = 0.796$). There were no significant differences in age, height, weight, FPG, HDL-C, triglycerides, BMI, and WC between patients with mild, moderate or severe OSA. The systolic and diastolic BP mean values were significantly higher in the group with severe OSA compared with the mild OSA group ($p = 0.042$ and $p = 0.036$, respectively).

Body composition, EFT, RVEDD and cIMT of all the patients and across AHI categories are shown in Table 1. The ranges of EFT, RVEDD and cIMT were 6–11.20 mm, 19–33 mm, and 0.6–1.2 mm, respectively. Trunk FM, arms FM and neck FM mean values were not significantly different among the three groups. There was a significant increase in EFT, RVEDD and cIMT with increasing severity of OSA. On the contrary, AHI higher values were most frequently detected in patients with the lowest leg FM.

We then evaluated the association between AHI and each single covariate by linear regression analysis. There was a positive association between AHI and EFT ($r = 0.536$; $p < 0.001$), RVEDD ($r = 0.480$; $p < 0.001$), cIMT ($r = 0.345$; $p < 0.001$) and trunk/leg FM ratio ($r = 0.330$; $p < 0.001$) (Fig. 1). In sex-stratified analyses, the likelihood of detection of higher EFT values was higher in men ($r = 0.571$; $p < 0.001$) than in women ($r = 0.359$; $p = 0.005$), with a progressive increase of sex difference at higher AHI values. Similar results were observed for RVEDD (men $r = 0.550$; $p < 0.001$ *vs.* women $r = 0.325$; $p = 0.012$). The r values for the cIMT-AHI correlation were almost superimposable for men ($r = 0.389$; $p = 0.003$) and women ($r = 0.326$; $p = 0.012$). The significance of linear regression between AHI and trunk/leg FM ratio was conserved in men ($r = 0.298$; $p = 0.026$) and was lost in women ($r = 0.192$; $p = 0.145$). There was no correlation between AHI and all the other variables evaluated except for WC ($r = 0.299$; $p = 0.025$) and neck FM ($r = 0.267$; $p = 0.046$) in men. A positive association, without gender differences, between EFT and RVEDD ($r = 0.759$; $p < 0.001$) was also observed.

Sex and age adjusted multivariate linear regression analyses for the associations between AHI and selected covariates are presented