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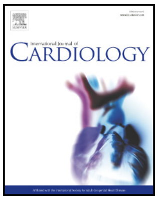

Pericardial and visceral, but not total body fat, are related to global coronary and extra-coronary atherosclerotic plaque burden

Gaston A. Rodriguez-Granillo *,[1], Exequiel Reynoso [1], Carlos Capunay [1], Jimena Carpio [1], Patricia Carrascosa [1]

Department of Cardiovascular Imaging, Diagnóstico Maipú, Buenos Aires, Argentina

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ABSTRACT

Background: To explore the relationship between coronary and extra-coronary atherosclerotic plaque burden with total and regional fat depots among patients undergoing ECG-gated aortic computed tomography angiography (CTA).

Methods: The subjects of this study comprised a cohort of consecutive patients who underwent ECG-gated thoracoabdominal CTA. We assessed the number of coronary segments with plaques (segment-involvement score, SIS); and the extra-coronary atherosclerotic plaque burden, comprising the aorta and supra-aortic trunks, iliofemoral arteries, and visceral arteries (extra-coronary SS). Total and regional fat volume (FV) were calculated.

Results: A total of 2700 vascular segments were evaluated in 90 patients. Obese patients ($n = 31$, 34%) showed similar coronary SIS ($p = 0.41$) and extra-coronary SS ($p = 0.22$) than non-obese patients. General body fat measurements were not related to atherosclerotic plaque burden scores, without associations between coronary or extra-coronary plaque burden and BMI ($p = 0.68$, and $p = 0.91$), abdominal circumference ($p = 0.13$, $p = 0.89$), total body FV ($p = 0.50$, $p = 0.98$), or abdominal FV ($p = 0.51$, $p = 0.99$). Pericardial FV was related to coronary SIS ($p < 0.0001$) and extra-coronary SS ($p = 0.008$), and visceral FV was related to the coronary SIS ($p = 0.006$) and extra-coronary SS ($p = 0.056$). Abdominal subcutaneous fat was inversely related to coronary SIS ($p = 0.038$) and extra-coronary SS ($p = 0.010$). Pericardial FV was identified as the only independent predictor of extensive coronary [OR 1.020 (95% CI 1.001–1.039), $p = 0.036$] and extra-coronary [OR 1.018 (95% CI 1.001–1.036), $p = 0.035$] plaque burden.

Conclusions: In the present study, pericardial and visceral fat were associated with an increased atherosclerotic burden, whereas we identified an inverse relationship between subcutaneous abdominal fat and plaque burden.

1. Introduction

The increased cardiovascular morbidity and mortality among obese patients is generally attributed to the association between obesity and several cardiovascular risk factors, as well as to the promotion of insulin-resistance and a pro-inflammatory state [1,2]. Notwithstanding, several studies including a meta-analysis of individual-level data have reported conflicting evidence comprising a negative correlation between coronary disease burden and the body mass index (BMI), as well as a decline in the association of obesity to years of life lost [3–5]. Moreover, among older adults, there is no clear relationship between obesity and mortality [6]. Such controversial or paradoxical behavior might be at least in part related to the rough definition of obesity based on the BMI, a poor index of adiposity [7–9]. Likewise, abdominal circumference is a good estimate of abdominal fat although it fails to distinguish between subcutaneous and visceral fat. On the contrary, regional adipose tissue (AT) deposits are related to divergent cardiometabolic profiles and prognosis, and can be measured accurately using computed tomography (CT). Overall, both visceral and pericardial fat have been associated with a worse prognosis, while subcutaneous abdominal fat may play, paradoxically, a beneficial role [10–12].

All these findings have been evaluated in individual reports exploring the relationship between specific regional fat depots and coronary or extra-coronary atherosclerosis [13]. Nevertheless, the association between global (coronary and extra-coronary) plaque burden and regional fat has not been elucidated. In our institution, CT angiograms (CTA) of the aorta involving the thoracic portion are performed using ECG-gating with dose modulation. This allows motion-free images of the thoracic aorta, enabling a higher diagnostic confidence compared to non-gated aortic CTA, as well as an accurate assessment of the coronary tree [14,15]. Accordingly, the purpose of this study was to explore the relationship between coronary and extra-coronary atherosclerotic plaque burden with total and regional AT depots among patients undergoing ECG-gated thoracoabdominal aortic CTA.

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* Corresponding author at: Department of Cardiovascular Imaging, Diagnóstico Maipú, Av Maipú 1668, Vicente López B1602ABQ, Buenos Aires, Argentina.
E-mail address: grodriguezgranillo@gmail.com (G.A. Rodriguez-Granillo).

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2. Methods

2.1. Study design and patient enrollment

This investigator-driven observational study comprised a cohort of consecutive patients aged between 33 and 87 years who underwent ECG-gated thoracoabdominal CTA in our institution between January 2016 and September 2017. Patients who refused to provide *Habeas data* were excluded. Among patients with repeated (follow-up) scans, only the first scan was included. Patients with previous endovascular aortic repair (EVAR), aortic bifemoral bypass, valve surgery, or coronary artery bypass graft (CABG) surgery were excluded. Patients were referred to our institution to undergo thoracoabdominal CTA for various indications including aortic dilatation, guidance of trancatheter aortic valve replacement, and atherosclerotic disease or suspicion of acute aortic syndrome (Appendix). A radiologist blinded to the CTA collected data regarding demographical characteristics and cardiovascular risk factors. The protocol was approved by the institutional ethics committee and all studies have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

2.2. Image acquisition

In our institution, CTA scans involving the thoracic aorta are acquired using ECG-gating techniques in order to avoid motion artifacts and to enable more accurate measurements [16]. Scans were acquired in three centers of the same institution using 64 ($n = 24$), 128 ($n = 15$), 256 ($n = 37$) slice CT scanners (Brilliance CT family; Philips Healthcare, Cleveland, USA) and a high definition CT ($n = 14$) scanner (Discovery HD 750, GE Medical Systems, Milwaukee, USA) with a single breath-hold from the supra-aortic trunks to the pubic symphysis. Among patients acquired using the high-definition scanner, the thoracic aorta CTA was acquired using ECG-gating, whereas abdominal non-gated CTA was performed immediately after the gated thoracic acquisition. Acquisition parameters were: 100–120 kV (according to the body mass index); 150–300 mAs (z-axis modulation was used on 64-, 128-, and 256-slice CT scanners); variable pitch; 0.5–0.75 rotation time; DFOV adjusted to the patient size; reconstructions using 1–1.5 mm slice thickness and 0.5 mm interval. Particular care was taken to acquire images with a sufficiently wide field of view in order to avoid missing (subcutaneous fat) data. CTA were acquired after intravenous administration of 80–100 mL of iodinated contrast (iobitridol, Xenetix 350TM, Guerbet, France) according to the BMI and body habitus. Angiograms were performed using a dual phase protocol, with the total undiluted contrast medium injected at a rate of 4–4.5 mL/s, followed by a 30 mL chasing bolus of normal saline at 3–4 mL/s.

2.3. Image analysis

Images were transferred to a dedicated workstation (Brilliance Workspace, Philips Healthcare, Cleveland, Ohio, USA), and analyses were performed by an experienced observer blinded to the clinical data. Two phases of the cardiac cycle were stored and available for the analysis, one systolic (37.5–40% of the R-R interval) and one mid-diastolic (75–78% of the R-R interval), and images were analyzed in the phase with the least motion artifacts. Axial planes, average multiplanar, and maximum intensity projection reconstructions (1–5 mm thickness) were used to assess the presence and extent of coronary and extra-coronary atherosclerotic plaque burden. The number of coronary segments with mixed or calcified plaques (segment-involvement score, coronary SIS) was calculated as previously described [17,18]. Methodological details regarding the assessment of coronary and extra-coronary plaque burden can be found in the appendix section. In brief, the extra-coronary atherosclerotic plaque burden comprised the presence and extent of disease in the thoracoabdominal aorta (including supra-aortic trunks), iliofemoral arteries, and visceral arteries. Thereafter, two scores were developed; one involving the number of regions involved (extra-coronary SIS), and other score (extra-coronary SS) involving both the extra-coronary SIS and a number of correction factors of orthogonal extension and severity (longitudinal and axial extension, degree of stenosis, and high-risk characteristics).

2.4. Anthropometric and regional fat measurements

Fat tissue was calculated using a semiautomated volumetric module dedicated software (Brilliance Workspace, Philips Healthcare, Cleveland, Ohio, USA), as previously defined, as tissue between −190 and −30 Hounsfield units [19]. Total body fat volume (FV) was assessed from the thoracic inlet to the cranial aspect of the femoral heads using a volume rendering technique, and all FV measurements were indexed to the body surface (cm^3/m^2). For FV measurements all automatically detected tissue were verified for accuracy and adjustments were made manually, and sequentially, in sagittal, coronal, axial views, and using the three dimensional rendered fat shell (Figs. 1–2). Visceral FV was defined as the fat enclosed by the visceral cavity, whereas subcutaneous abdominal FV was defined as the difference between abdominal FV and visceral FV. Pericardial FV measurements comprised slices between 15 mm above the cranial border of the left main coronary artery and the diaphragm. The anterior edge was defined by the chest wall and the posterior edge by the aorta and the bronchus (the posterior mediastinum was excluded). In order to avoid intricate visualization of the pericardium particularly among lean patients, pericardial FV involved both epicardial and paracardial fat. In this regard, the MESA study has shown a very high correlation between pericardial and epicardial fat [20]. Finally, subcutaneous abdominal AT thickness (anterior plus posterolateral thickness) was measured at the level of the abdominal circumference measurement (coincident with cranial border of the iliac crest).

2.5. Statistical analysis

Discrete variables are presented as counts and percentages. Continuous variables are presented as means ± SD, or median (interquartile range), as indicated. Comparisons between continuous variables were performed using independent samples *t*-test, one-way analysis of variance, and Bonferroni (post-hoc comparisons) tests, as indicated. Comparisons between categorical variables were performed using chi-square tests. Correlations between continuous variables were assessed using Pearson correlation coefficients. On the basis of an interim analysis showing that the mean coronary SIS was 2.5 and 5.0 at the lowest and highest pericardial FV tertiles, we calculated a sample size of 29 subjects per tertile ($n = 87$ overall) in order to achieve a power of 80% to detect a true difference in population means, considering a type I error of 0.05 (two-sided), a SD of 2.5 in the lowest tertile and of 4.0 in the highest tertile. Logistic regression analysis was performed to identify potential predictors of extensive coronary plaque burden (coronary SIS >5), and of an extra-coronary SS >12.85 (upper tertile) including the following variables in the model (enter method): sex, age, hypercholesterolemia, hypertension, diabetes, smoking, total body FV (cm^3/m^2), pericardial FV (cm^3/m^2), visceral FV (cm^3/m^2), and subcutaneous abdominal fat thickness (mm). In order to assess the interobserver agreement for the assessment of regional FV, coronary, and extra-coronary plaque burden, 20 cases were randomly selected and re-analyzed independently by two observers. These data were analyzed using intraclass correlation coefficients (ICC; two-way random effect model, absolute agreement, and average measurement) with 95% confidence intervals. A two-sided p value of <0.05 indicated statistical significance. Statistical analyses were performed using SPSS software, version 22.0 (IBM SPSS Statistics for Windows, Armonk, NY) and MedCalc Software (Ostend, Belgium).