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Metabolic syndrome impact on cardiac autonomic modulation and exercise capacity in obese adults

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ABSTRACT

Obesity is often associated with increased risk of cardiometabolic morbidities and mortality. However, evidence shows that some obese individuals are more likely to develop such risk factors early in life, including those with Metabolic Syndrome (MetS). Whether the presence of MetS in obese people impairs cardiac autonomic modulation (CAM) remains to be investigated.

Methods: Cross-sectional study. Sixty-six subjects were classified as normal-weight (NW, n = 24) or obese (BMI ≥ 30 $kg{\cdot}m^{-2}$): metabolically healthy (MHO, n = 19) *vs* unhealthy (MUHO, n = 23: NCEP/ATPIII-MetS criteria). Body composition (bioimpedance), metabolic (glucose-insulin/lipid) and inflammatory profiles were determined. Linear and nonlinear heart rate variability (HRV) indices were computed at rest and during the submaximal six-minute step test (6MST). Blood pressure (BP) and metabolic and ventilatory variables were assessed (oxygen uptake, VO_2; carbon dioxide production, VCO_2; minute ventilation, V_E) during the 6MST and the maximal cardiopulmonary exercise testing (CPX).

Results: All groups reached the same 6MST intensity (VO_2 ~ 80% and HR ~ 87% of CPX peak values). Both obese groups, independently of MetS, presented higher BP and lower maximal VO_2 than NW. However, HRV differed between groups according to MetS at rest and during exercise: MUHO had lower meanRRi and SD1 than NW and lower RMSSD and pNN50 than MHO at rest; during exercise, the lowest SDNN, TINN, SD1 and Shannon entropy were observed for MUHO. Significant correlations were found between MetS, insulin resistance and HRV indices; and between insulin resistance and aerobic capacity (VO_{2peak}).

Conclusion: Obesity *per se* impairs aerobic-hemodynamic responses to exercise. However, MetS in obese young adults negatively impacts overall HRV, parasympathetic activity and HRV complexity.

1. Introduction

Obesity has been associated with physical disability and an increased risk of cardiometabolic diseases and mortality (Capodaglio et al., 2014; Rana et al., 2007). However, recent evidence has shown that not all obese people are at increased health risk. The "metabolically healthy obese (MHO)" concept has emerged to refer to those individuals who, although presenting excessive fat mass, do not develop as many health complications as expected (Phillips, 2013).

Although still controversial, most studies point to the Metabolic Syndrome (MetS) as the determinant of an unhealthy metabolism, since it is characterized by the clustering of metabolic abnormalities that are each, individually, associated with increased risk of chronic diseases (American Medical Association, 2001). In addition, further metabolic impairment appears to be influenced by the development of obesity-related low grade inflammation and impaired glucose-insulin metabolism, more specifically insulin resistance (Phillips, 2013).

It has been demonstrated that poor cardiac autonomic modulation (CAM), cardiorespiratory fitness (CRF) and sedentary lifestyle are independently associated with MetS (Lakka et al., 2003; Lee et al., 2010;

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Whaley et al., 1999) and adverse cardiovascular outcomes (Franklin & McCullough, 2009; Wulsin et al., 2015). Therefore, these factors seem to play an important intermediate role in increasing cardiovascular mortality risk in obese adults with metabolic disorders (Thayer et al., 2010).

To date, it is known that obesity (Rossi et al., 2015) and the presence of metabolic disorders lead to decreased overall autonomic variability and sympathetic overactivity at rest (Tentolouris et al., 2008), but it remains unclear whether more complex autonomic responses, such as during exercise, are impaired in obese individuals with MetS. Physical exercise has been considered as a powerful autonomic test that can evaluate simultaneously sympathetic and parasympathetic modulatory responses in obese populations (Castello et al., 2011; Lind & Andren, 2002). Heart rate variability (HRV) has been suggested as an easy and cost-effective method for evaluating populations at risk of presenting autonomic impairment (Vanderlei et al., 2009). A previous populational study (Felber Dietrich et al., 2008) demonstrated that healthy obese people (*i.e.* who regularly practiced physical activity ≥ 2 h per week) had a 13% higher positive effect on overall HRV during activities of daily living. However, evidence demonstrating the influence of metabolic syndrome in obese people on CAM, especially in response to submaximal exercises (as most of the functional activities we perform on a daily basis), is still lacking.

Functional field tests, such as the six-minute step test (6MST), have been gaining great clinical interest to evaluate physiological responses and limitations as they mimic functional daily activities. The 6MST presents some advantages over the six-minute walking test as it is a reliable test in healthy individuals (Arcuri et al., 2015), it presents acceptable agreement (validity) when compared to the maximal aerobic capacity in obese people (Carvalho et al., 2015; Di Thommazo-Luporini et al., 2015) and it promotes more stable conditions to evaluate HRV than the maximal exercise testing (CPX) due to its reported near-maximal characteristic and stable self-selected cadence. Also, the CPX is hardly ever accessible in clinical practice due to staff and cost requirements and it imposes difficulties to assess HRV because of its incremental nature.

Therefore, the main objective of this study was to investigate the influence of MetS in adults with obesity on CAM at rest and in response to a submaximal functional exercise. The secondary objective was to investigate the associations between MetS, glucose metabolism and inflammatory markers and CAM.

2. Materials and methods

2.1. Study participants

This cross-sectional study included men and women aged 20–45 years recruited from the community *via* social communication (radio, television, flyers, email to employees and students of the university and contact with nutritionists and physicians). Participants were recruited and enrolled in the study from April 2013 to July 2015 and were non-randomly allocated into the normal-weight group (NW, n = 24), the metabolically healthy but obese group (MHO, n = 19) and the metabolically unhealthy obese group (MUHO, n = 23) according to their Body Mass Index (BMI): 1) NW ≤ 25 kg·m^{-2}; and 2) MHO and MUHO ≥ 30 kg·m^{-2}. Subjects were subsequently classified as MUHO if they presented MetS according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria (American Medical Association, 2001), *i.e.* when 3 out of 5 of the following risk determinants are present: waist circumference > 120 and > 88 cm or high-density lipoprotein cholesterol (HDL) < 40 and < 50 mg/dL for men and women, respectively; triglycerides > 150 mg/dL; blood pressure ≥ 130/≥ 85 mm Hg; and fasting glucose ≥ 110 mg/dL. All tests were performed within four non-consecutive days (at least 48 h-interval between them).

Eligibility criteria to participate in this study were: present stable body weight for at least 6 months; perform < 150 min/week of structured physical activity; not being pregnant or in premature menopause; not having undergone gynecological and/or orthopedic surgeries; non cigarette smokers or stopped smoking for at least 1 year; non-alcohol drinkers; not using drugs influencing the autonomic nervous system; not having a diagnosis of any chronic disease and/or cognitive impairment. Exclusion criteria after study initiation were: difficulty in understanding experimental procedures; and/or intolerance to withdrawal of stimulants prior to the evaluations (*e.g.* coffee and chocolate derivatives).

The authors conducted the study after obtaining the Institutional Ethics Committee approval (CEP-UFSCar N.326.607) for human research. All volunteers agreed and signed a written informed consent.

2.2. Clinical evaluation

The first visit included an evaluation of clinical and medical history, assessment of physical activity level by the Baecke questionnaire, and body distribution and composition: height (Welmy 104-A, Santa Barbara d'Oeste, Sao Paulo, Brazil), body mass (BM), waist circumference (WC) and fat mass (FM) by means of a tetrapolar bioelectrical impedance analyzer (Model BC-558, Ironmann/Tanita Corporation, Tokyo, Japan). Baseline systolic and diastolic blood pressure (BP) were measured to the nearest 2 mm Hg with the patient in a sitting position for at least 10 min.

Pulmonary function was assessed (Oxycon Mobile®, Mijnhardt/Jager, Wurzburg, Germany) to ensure inclusion of volunteers with no airflow obstruction according to the normative values.

2.3. Metabolic and inflammatory profile

Volunteers were instructed to fast 12 to 14 h and blood collection was carried out in the morning. The volunteers were oriented not to exercise within 48 h prior to the exam, to maintain their usual diet and not to attend the exam with any known inflammatory process or after having taken any unusual medication.

Fasting plasma glucose and insulin levels and the indirect indices of insulin resistance (Homeostasis Model Assessment method, HOMA-IR) and sensitivity (quantitative insulin sensitivity check index, QUICKI); and lipid profile (high density lipoprotein- [HDL-c], low density lipoprotein- [LDL-c], very low density lipoprotein- [VLDL-c] cholesterol; and triglycerides [TGL]) were quantified.

A blood subsample was stored in heparinized tubes, centrifuged and aliquots obtained from plasma were frozen at −80 °C for subsequent analysis. Samples were analyzed in duplicate by the enzyme-linked immunosorbent assay (ELISA) method. Human total adiponectin/Acrp30 (ADP), leptin (LP) and Tumor necrosis factor-α (TNF-α) were determined by the Quantikine® Human Immunoassays (R&D Systems, Minneapolis, USA); serum levels of interleukin 6 (IL-6) and 10 (IL-10) were determined by the ELISA MAX™ Standard Set (BioLegend, San Diego, Canada). Serum concentrations of LP, TNF-α, IL-6, IL-10 (pg/mL) and ADP (ng/mL) were determined by interpolation from a standard curve according to the manufacturer's recommendations.

2.4. Cardiac autonomic modulation

The heart rate signal and the RR intervals (RRi) for analysis of heart rate variability (HRV) were acquired by a Polar S810i monitor (Polar Electro, Kempele, Finland).

Data collection was performed in a room with a temperature between 21 and 23 °C and humidity of 40–60%. The environment was controlled so as to avoid the participant's anxiety (closed room with no noise or movement of people around). A capture strap was positioned on the anterior chest of the volunteer and the receptor (Polar S810i) on the wrist and the subject was oriented not to talk or move abruptly during the test. They were instructed to lie in a supine position on a mat and to breathe spontaneously for 15 min.