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Clinical implication of body size phenotype on heart rate variability

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ABSTRACT

We compared heart rate variability (HRV) values according to the following body size phenotypes: metabolically healthy normal weight (MHNW), metabolically unhealthy but normal weight (MUNW), metabolically healthy but obese (MHO), and metabolically unhealthy obese (MUO). We retrospectively analyzed a dataset from 1200 participants who had visited the Cardiovascular Center at Korea University Guro Hospital between March 2009 and February 2014 and underwent Holter monitoring for 24 h. HRV was calculated from standard deviation of normal-to-normal R-R intervals (SDNN), standard deviation of the average normal-to-normal intervals (SDANN), and root mean square of successive differences (rMSSD) measurements, and study subjects were classified according to body mass index (BMI) and presence or absence of metabolic syndrome. Various HRV indices, including SDNN, SDANN, and rMSSD, were significantly lower in MUNW subjects than in MHNW or MHO subjects, while there were no significant differences between MUNW and MUO subjects. Although BMI had no significant correlation with any HRV indices, SDNN, SDANN, and rMSSD values had significant negative correlations with waist circumference and levels of C-reactive proteins, AST, ALT, fasting glucose, and HOMA-IR. A significant positive correlation was observed between HRV index and HDL level. Furthermore, the SDNN value significantly decreased with an increase in the number of metabolic syndrome components after adjusting for other covariates.

Abbreviations: HRV, heart rate variability; MHNW, metabolically healthy normal weight; MUNW, metabolically unhealthy but normal weight; MHO, metabolically healthy but obese; MUO, metabolically unhealthy obese; SDNN, standard deviation of normal-to-normal R-R intervals; SDANN, standard deviation of the average normal-to-normal intervals; rMSSD, root mean square of successive differences; BMI, body mass index; CVD, cardiovascular disease; CRP, C-reactive proteins; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; ARBs, angiotensin receptor blockers; ACE, angiotensin converting enzyme.

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Compared to MHNW or MHO subjects, Korean men and women with the MUNW phenotype exhibited decreased HRV, suggesting that low HRV is related to adverse cardiovascular outcomes in MUNW individuals.

1. Introduction

The autonomic nervous system contributes to nearly every important homeostatic process in the body. The earliest manifestation of cardiac autonomic dysfunction is a decrease in heart rate variability (HRV), which is a physiological variation in the interval between heartbeats. High HRV is an indication of good health and reflects the heart's ability to adapt to environmental stress [1], whereas lower HRV is related to sudden cardiac death and a higher risk of all-cause mortality in survivors of an acute myocardial infarction [2,3]. Obesity is a well-known risk factor of low HRV and overstimulation of the sympathetic nervous system [4]. Landsberg et al. [5] suggested that, during the development of obesity, hyperinsulinemia increases sympathetic activity in order to limit further weight gain. Obese subjects have higher basal sympathetic activities and a blunted response to sympathetic stimuli, which is characteristic of inflexible HRV [6,7]. Therefore, a distorted modulation in autonomic tone may influence the increase in cardiovascular risk associated with obesity.

However, the adverse cardiovascular events are diverse among obese individuals [8]. Recent studies have focused on individuals with phenotypes that show a non-linear relationship between body mass index (BMI) and adverse clinical outcome, such as metabolically healthy obese (MHO) and metabolically unhealthy but normal weight (MUNW) phenotypes. For instance, Appleton et al. [9] showed that MHO subjects were no more likely to develop cardiovascular disease (CVD) than were metabolically healthy normal weight (MHNW) individuals. On the other hand, Meigs et al. [10] reported that MUNW subjects had a two- to three-fold increased risk of CVD events relative to MHNW subjects. These results suggest that a generalized obesity index such as BMI cannot fully reflect the risk of obesity-related cardiovascular complications [11]. Despite having a high BMI, MHO people are characterized as having high insulin sensitivity, normal blood pressure, and favorable lipid, inflammatory, and adipokine profiles [12], while MUNW subjects have atherogenic lipid profiles, high blood pressure, higher proportion of visceral fat and lower proportion of lean body mass [13]. Therefore, determining the underlying mechanism that differentiates MHO from MUNW individuals may allow for the identification of novel therapeutic targets of CVD.

Until now, there has been no study that compared the HRV values of MHNW, MUNW, MHO and metabolically unhealthy obese (MUO) groups. Because of the well-established role of HRV in CVD, we hypothesized that HRV value could predict the different cardiovascular outcomes in individuals with different body size phenotypes. Therefore, we compared HRV values based on body size phenotype and adjusted for age, gender, alcohol, smoking, and medications that might affect HRV. Furthermore, we examined the relationships of HRV with insulin resistance, low-grade systemic inflammatory markers (C-reactive proteins; CRP), and abdominal obesity.

2. Methods

2.1. Study Design and Participants

We retrospectively analyzed data from 1390 subjects who consecutively visited the Cardiovascular Center at Korea University Guro Hospital for chest discomfort between March 2009 and February 2014 and underwent 24-h Holter monitoring. Participants were healthy Korean men and women between 20 and 80 years of age, residing in Seoul, South Korea. Subjects were excluded from this study if they met any of the following criteria: history of CVD (myocardial infarction, unstable angina, stroke, or cardiovascular revascularization); evidence of cardiac disease on clinical examination; abnormal results on electrocardiogram, stress test, or echocardiogram; stage 2 hypertension (resting blood pressure ≥ 160/100 mmHg); history of inflammatory conditions that would affect the study results; use of medications that might affect inflammatory status, including steroid and non-steroidal anti-inflammatory drugs within the previous six months; or malignancy or severe renal or hepatic disease. Medical history and lifestyle information were collected from 1200 subjects using a detailed questionnaire. The Korea University Institutional Review Board approved this study protocol in accordance with the Declaration of Helsinki (KUGH15252).

2.2. Definitions of Body Size Phenotypes

Study subjects were classified according to BMI and presence or absence of metabolic syndrome (MetS). Obesity was defined based on criteria from the Korean Society for the Study of Obesity, which defines "normal" as a BMI between 18.5 and 25.0 kg/m^2 and "obese" as a BMI greater than 25.0 kg/m^2 [14]. MetS was defined according to the criteria established by the National Cholesterol Education Program Adult Treatment Panel III using the adjusted waist circumference for Asians [15]. The criteria require the presence of three or more of the following components: (1) high blood pressure (systolic blood pressure ≥ 130, diastolic blood pressure ≥ 85 mmHg, or known treatment for hypertension), (2) hypertriglyceridemia (fasting plasma triglycerides ≥1.69 mmol/L), (3) low HDL cholesterol (fasting HDL cholesterol <1.04 mmol/L in men, <1.29 mmol/L in women), and (4) hyperglycemia (fasting plasma glucose ≥5.6 mmol/L or known treatment for diabetes). By combining the BMI and MetS groups, all study subjects were classified into four groups: normal weight without MetS (MHNW), normal weight with MetS (MUNW), obese without MetS (MHO), and obese with MetS (MUO).

2.3. Anthropometric and Laboratory Measurements

BMI was calculated as weight/height^2 (kg/m^2), and waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest. All blood