

The Association between Central Adiposity and Autonomic Dysfunction in Obesity

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Key Words

Epicardial fat thickness · Waist circumference · Body mass index · Autonomic nervous system

Abstract

Objective: To determine the relationship between central adiposity parameters and autonomic nervous system (ANS) dysfunction. **Subjects and Methods:** The study included 114 obese individuals without any cardiovascular risk factors. Weight (in kg), height (in m), and waist circumference (WC; in cm) were measured and body mass index was calculated. Echocardiographic examination was performed to measure left ventricular mass and epicardial fat thickness (EFT). All the participants underwent an exercise test and electrophysiological evaluation using electromyography. Heart rate recovery (HRR) at 1–5 min, R-R interval variation at rest and during hyperventilation, and sympathetic skin response were measured. Pearson's correlation analysis was used. Multiple linear regression analysis was used to identify the factors associated with autonomic dysfunction. **Results:** The HRR at 1–5 min was negatively correlated with WC and age (WC-HRR1: $r = -0.32$; WC-HRR2: $r = -0.31$; WC-HRR3: $r = -0.26$; WC-HRR4: $r = -0.23$; WC-HRR5: $r = -0.21$; age-HRR2: $r = -0.32$; age-HRR3: $r = -0.28$; age-HRR4: $r = -0.41$; age-HRR5: $r =$

-0.42). Age was the only independent predictor of reduced HRR at 1–5 min. In addition, WC predicted a reduced HRR at 3 min. There were no significant associations between central obesity and electrophysiological parameters. EFT was not associated with ANS dysfunction. **Conclusion:** In this study, central adiposity and aging were associated with ANS dysfunction in obese individuals. The WC could be a marker of ANS dysfunction in obese individuals without any cardiovascular risk factors. The HRR assessment at a later decay phase could be more valuable for evaluating ANS function than during early recovery.

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Introduction

The autonomic nervous system (ANS) is thought to contribute to the pathophysiology of obesity [1]. Increased adiposity had been linked to alterations in both sympathetic and parasympathetic activities [1, 2]. Decreased adiposity after weight reduction has also been associated with improved ANS function [3, 4]. Autonomic dysfunction can be assessed by various techniques, including heart rate variability (HRV), heart rate recovery (HRR), sympathetic skin response (SSR), and R-R interval variation

(RRIV) [5]. The ability of specific measures of total or regional body fat distribution, such as body mass index (BMI), waist circumference (WC), percent body fat, and visceral adipose tissue volume – in relation to HRV – to predict ANS function has been studied [6–8]. Findings concerning the relationship between BMI and HRV have been inconsistent [9, 10]. HRR, defined as the change in heart rate following exercise, is an indicator of cardiac autonomic function and has been validated as a predictor of mortality [11]. Epicardial fat thickness (EFT) is strongly correlated with visceral obesity, metabolic syndrome, diabetes mellitus, and cardiovascular disease [12]. EFT can be measured using standard 2-dimensional echocardiography. The precise pathophysiology and mechanisms underlying increased mortality unrelated to cardiovascular risk factors associated with obesity remain unknown. A better understanding of the link between central adiposity parameters (i.e. EFT, WC) and autonomic dysfunction could help elucidate the mechanisms by which central adiposity contributes to the risk of cardiovascular morbidity and mortality. The hypothesis of the present study was that parameters of central adiposity – including EFT – measured by echocardiography might be related to autonomic dysfunction in obesity. Hence, the aim of the present study was to evaluate autonomic function based on HRR, SSR, and RRIV, and to examine their relationships with parameters of central adiposity in obese individuals without any cardiovascular risk factors.

Subjects and Methods

Patients

The study included 114 self-referred consecutive obese patients for weight loss. A power analysis was performed before the study. Accordingly, when effect size was considered moderate, 80 subjects would have resulted in 95% confidence and 90% power. We included 114 subjects in the current study. The power analysis showed that our results when examined for significant correlations reached 95% confidence and 95% power. Exclusion criteria were cardiovascular disease (acute coronary syndrome, angina pectoris, any visible stenosis >20% in at least 1 coronary artery by angiography, percutaneous or surgical revascularization, stroke, transient ischemic attack, and peripheral arterial disease), moderate (>2+) valvular regurgitation or any valvular stenosis, any rhythm other than sinus rhythm, systolic dysfunction (ejection fraction <50%), insufficient echocardiographic imaging, myocardial wall thinning or motion abnormalities (by echocardiography and suggestive of previous myocardial infarction), anemia, renal failure, hepatic failure, pregnancy or lactation, current or past smoking, regular use of alcohol, any systemic inflammatory condition, history of conventional cardiovascular risk factors (including diabetes mellitus, obstructive sleep apnea, hypertension, hyperlipidemia, and metabolic syndrome), major systemic or psychiatric disease, and use of

any medication due to the potential confounding effects on ANS function. The study protocol was approved by the Medical Ethics Committee of the participating university and was performed in accordance with the Declaration of Helsinki, and all participants provided written informed consent. Unfortunately, we were not able to recruit a control group because the ethics committee would not allow us to perform painful invasive electrophysiological evaluation on healthy subjects.

The participants were weighed in kg and their height was measured in m; then BMI was calculated. Obesity was defined as BMI >30. WC (cm) was measured midway between the lowest rib and the iliac crest while the participants were standing upright. Fasting plasma glucose and insulin levels were obtained on all participants. Then the homeostasis model assessment (HOMA) index was calculated using the following formula: (fasting plasma glucose × fasting plasma insulin)/22.5 [13]. The state of insulin resistance was determined using the cutoff value of 2.7.

Exercise Treadmill Test

All the participants underwent exercise testing, with the goal of achieving ≥85% of the age-predicted maximum heart rate according to the standard or modified Bruce protocol [14]. The participants were encouraged to exercise until they experienced limiting symptoms. Peak exercise was followed by a 2-min cooling down period of walking at 1.5 mph at a grade of 2.5%, as previously reported [15]. During each exercise stage and every minute for 5 min during recovery, blood pressure, heart rate, and cardiac rhythm were recorded. HRR at 1–5 min was defined as the difference between the heart rate during peak exercise and at 1–5 min of the recovery period. Typical anginal chest pain, >1 mm depression/elevation of the ST segment, and arrhythmias were not observed in any of the participants during the exercise test.

Echocardiographic Analysis

Echocardiographic examination at rest was performed in each participant while in the left lateral decubitus position, using standard views and a Vivid 7 echocardiography device (GE-Vingmed, Horten, Norway). Left ventricular mass (LVM), the LVM index, and LV wall thickness were calculated from 2-dimensional guided M-mode echocardiographic tracings obtained at the midchordal level in the parasternal long-axis view, according to American Society of Echocardiography criteria [16]. All echocardiographic findings were analyzed by a single cardiologist (Y.T.Y.) who was blinded to clinical and laboratory characteristics of the patients. Intraobserver variability <5% was accepted for the echocardiographic measurement. The LVM index was calculated using the corrected American Society of Echocardiography simplified cubed equation, and was indexed for body surface area using the software package of the device [17]. Epicardial fat was considered the echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium, and EFT was measured perpendicularly on the free wall of the right ventricle at end-systole in 3 cardiac cycles, as previously described [18]. The mean value of 3 cardiac cycles from 2 echocardiographic views was calculated.

Electrophysiological Evaluation

Electrophysiological evaluation of RRIV and SSR was performed using a Medelec Synergy Nicolet EDX EMG device, according to a protocol recommended by the International Federation of Clinical Neurophysiology [19].

RRIV Measurement

For heart rate variation during resting, the participants underwent recording during 5 min of resting. For heart rate variation in response to breathing, the heart rate was recorded while the patients were breathing deeply at a rate of 6 breaths min^{-1} (inhalation: 5 s; expiration: 5 s). After 8 deep breaths, each participant rested for 5 min and the test was repeated. The mean value of 2 recordings was calculated.

Recordings were made using 2 disc electrodes placed on the dorsum of each hand; filter settings were 20–100 Hz, sensitivity was 100 μV , and the sweep speed was 2 s division^{-1} . The RRIV was calculated using the formula, $a/b \times 100$, where 'a' is the difference between the earliest and the latest appearing responses, and 'b' is the mean R-R interval. RRIV responses at rest and deep breathing were considered abnormal if >2 SD lower than the age-adjusted mean response in a normal population [5]. The ratio of RRIV during hyperventilation (HV) to RRIV at rest was defined as the HV-RRIV ratio, and the difference between RRIV during HV and at rest was defined as the HV-RRIV difference.

SSR Measurement

For palmar SSR, the median nerve was stimulated at a strength ≥ 3 -fold that of sensory threshold for 0.2 ms at 1 min^{-1} to avoid habituation, using disc electrodes placed on the palmar and dorsal surfaces of both hands; the filter settings were 0.2–100 Hz, sensitivity was 500 μV , and the sweep speed was 10 s division^{-1} . Amplitude was measured peak to peak. The response was considered absent if no consistent voltage change occurred using a sensitivity of 50 mV division^{-1} . Additionally, amplitude was considered abnormal when ≥ 2 SD below the mean laboratory value.

Statistical Analysis

Statistical analysis was performed using SPSS v.18.0 for Windows (SPSS Inc., Chicago, Ill., USA). Continuous and categorical data are shown as means \pm SD and percentages, respectively. The distribution of data was checked with a Kolmogorov-Smirnov test and, accordingly, Pearson's correlation analysis was used to detect the relationship between continuous variables. Multiple linear regression analysis was used to identify the factors associated with autonomic dysfunction. The level of statistical significance was set at $p < 0.05$. A multiple linear regression model was constructed to determine the relationship between the clinical and laboratory findings, and autonomic dysfunction.

Results

The mean age of the 114 obese patients was 41.03 ± 12.2 years and the mean BMI was 38.26 ± 6.35 . Clinical and laboratory characteristics of the 114 participants are shown in table 1. There were weak significant negative correlations between HRR at 1–5 min, and WC and age (WC-HRR1: $p = 0.001$, $r = -0.32$; WC-HRR2: $p = 0.002$, $r = -0.31$; WC-HRR3: $p = 0.01$, $r = -0.26$; WC-HRR4: $p = 0.02$, $r = -0.23$; WC-HRR5: $p = 0.04$, $r = -0.21$; age-HRR2: $p = 0.001$, $r = -0.32$; age-HRR3: $p = 0.004$, $r = -0.28$; age-HRR4: $p = 0.0001$, $r = -0.41$; age-HRR5: $p = 0.0001$, $r =$

Table 1. Clinical and laboratory characteristics of subjects ($n = 114$)

	Mean \pm SD	Median	Range
Age, years	40.9 \pm 12.27	41.5	17–65
Male, n (%)	18 (16.1)	–	–
WC, cm	105.65 \pm 11.42	104	83–129
BMI	38.08 \pm 6.27	37	30–54
Systolic blood pressure, mm Hg	123.27 \pm 13.37	120	100–139
Lifetime ASCVD risk, % ¹			
Women	28.81 \pm 11.61	27	8–39
Men	37.7 \pm 12.1	41	5–46
Laboratory measurements			
Total cholesterol, mg/dl	188.19 \pm 31	190	117–239
HDL-C, mg/dl	49.6 \pm 14.5	48	5–91
LDL-C, mg/dl	111.81 \pm 27.4	112	55–159
Triglycerides, mg/dl	132.15 \pm 59.39	121	39–299
Fasting glucose, mg/dl	92.65 \pm 5.82	94	68–99
Insulin, $\mu\text{IU/ml}$	15.03 \pm 8.33	12.23	3.3–43.5
HOMA	3.46 \pm 1.99	2.77	0.7–10.2
Creatinine, mg/dl	0.65 \pm 0.13	0.60	0.4–1.1

¹ Lifetime risk estimates for atherosclerotic cardiovascular disease according to the race- and sex-specific pooled cohort equations, $p = 0.015$.

–0.42). There was also a weak significant negative correlation between age and the HV-RRIV ratio ($p = 0.03$, $r = -0.22$), and between age and the HV-RRIV difference ($p = 0.04$, $r = -0.21$). There were no correlations between clinical and laboratory characteristics and RRIV, the HV-RRIV ratio, and the HV-RRIV difference (table 2). Pearson's correlation coefficients between WC and HRR at 1–5 min are shown in fig. 1.

The multiple linear regression model showed that age was the only independent predictor of reduced HRR at 1–5 min, whereas age and WC were independent predictors of HRR at 3 min (table 3).

Discussion

The findings showed that as a measure of central adiposity WC, but not EFT, was associated with greater ANS dysfunction. This relationship was observed primarily in terms of sympathetic activity. Overall adiposity, based on BMI, was not associated with either HRR or electrophysiological parameters. Thus, abdominal adiposity, as opposed to overall adipose tissue, could adversely affect ANS function.

Table 2. Relationships between clinical and laboratory characteristics and HRR at 1–5 min, RRIV, and during HV, the HV-RRIV ratio, and the HV-RRIV difference

	HRR1		HRR2		HRR3		HRR4		HRR5		RRIV		HV		Ratio		Difference	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Age	-0.19	0.06	-0.32	0.001	-0.28	0.004	-0.41	0.0001	-0.42	0.0001	0.1	0.32	0.003	0.97	-0.22	0.03	-0.21	0.04
BMI	-0.16	0.12	-0.19	0.06	-0.06	0.54	-0.06	0.55	-0.07	0.5	0.1	0.34	0.04	0.66	-0.13	0.22	-0.1	0.35
WC	-0.32	0.001	-0.31	0.002	-0.26	0.01	-0.23	0.02	-0.21	0.04	0.06	0.59	0.003	0.97	-0.08	0.43	-0.1	0.33
NLR	0.1	0.38	0.15	0.18	0.15	0.18	0.15	0.16	0.17	0.13	-0.15	0.17	-0.05	0.66	0.15	0.17	0.05	0.67
PLR	0.14	0.21	0.2	0.07	0.15	0.16	0.21	0.06	0.24	0.03	-0.22	0.05	-0.16	0.16	0.16	0.14	-0.05	0.66
HOMA	-0.09	0.36	-0.06	0.58	-0.04	0.67	-0.08	0.41	-0.06	0.56	-0.09	0.38	-0.12	0.24	-0.02	0.85	-0.08	0.42
LVM index	-0.09	0.4	-0.08	0.4	-0.05	0.62	-0.06	0.54	-0.11	0.26	0.07	0.48	-0.02	0.81	-0.18	0.07	-0.12	0.24
Mean EFT	-0.05	0.63	-0.09	0.42	-0.04	0.7	-0.13	0.24	-0.2	0.07	0.18	0.1	0.05	0.63	-0.2	0.06	-0.09	0.41

NLR = Neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio.

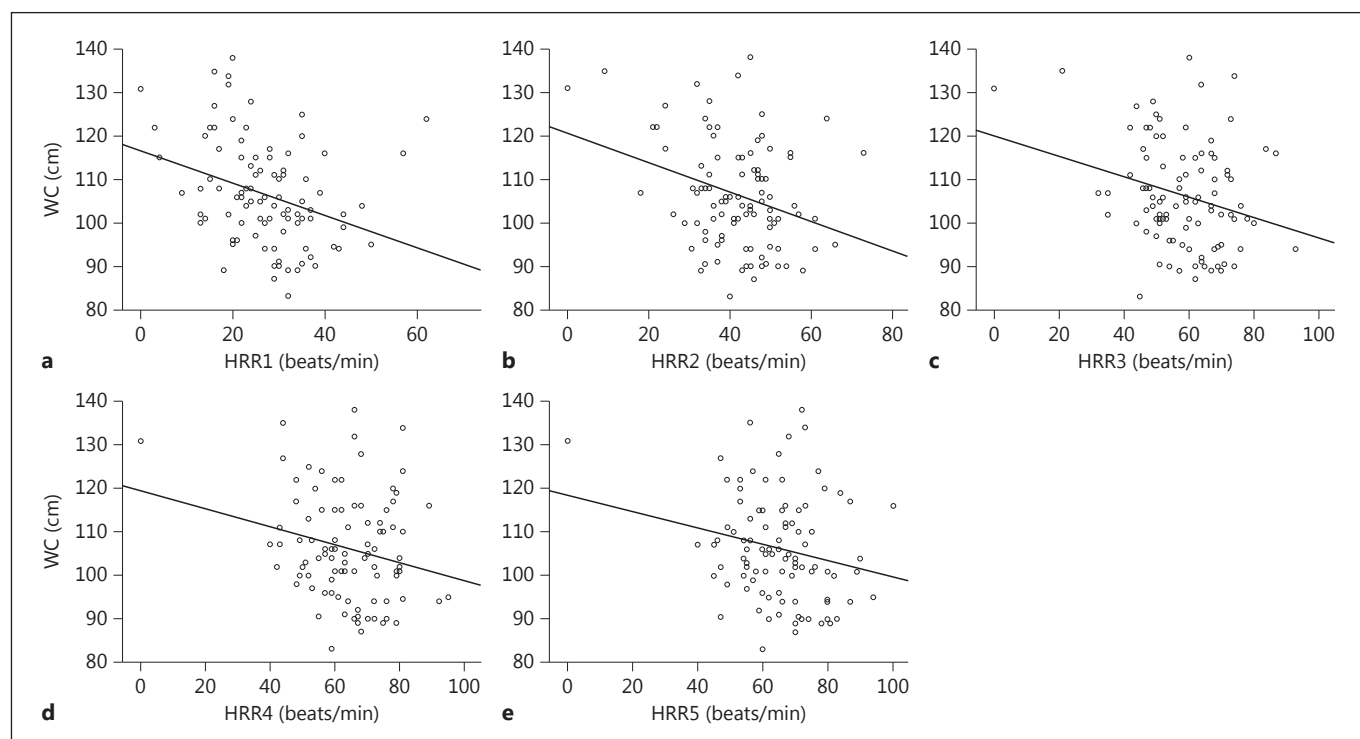


Fig. 1. a–e Correlation between WC and HRR at 1–5 min.

In this study, WC and age were associated with HRR at 1–5 min as reported in other studies [6–8, 20, 21], obesity measurements were differently associated with HRV, WC was negatively correlated with HRV measurements, and WC predicted slower HRR at 3 min after exercise. Lindmark et al. [20] reported that there was a positive correlation between visceral abdominal fat and a high sympathetic-parasympathetic ratio based on HRV assessment, whereas subcutaneous abdominal fat was not associated with HRV measures. Christou et al. [21] ob-

served higher abdominal to peripheral body fat distribution measured via dual-energy X-ray absorptiometry in young and old healthy males, which was strongly correlated with lower sympathetic and parasympathetic function that explained a significant portion of several aging-related changes in ANS. Windham et al. [8] reported that increasing WC, but not BMI, was associated with decreasing HRV variables in younger participants. Central adiposity might contribute to ANS declines early in life. A large-scale cross-sectional study that included appar-

Table 3. Multiple linear regression analysis to determine the independent predictors of autonomic dysfunction in obese subjects

	B	Odds ratio	95% CI (lower to upper)	p
<i>HRR1 (R² = 0.56; p = 0.0001)</i>				
Cons	149.4	–	118.2 to 180.7	0.000
Age	–0.9	–0.6	–1.2 to –0.6	0.000
LR	0.2	0.1	–0.1 to 0.5	0.179
BMI	–0.2	–0.1	–0.9 to 0.5	0.487
WC	0.2	0.1	–0.2 to 0.6	0.335
HOMA	–0.8	–0.1	–2.7 to 1.1	0.388
M.Eft	0.4	0	–1.5 to 2.3	0.684
<i>HRR2 (R² = 0.58; p = 0.0001)</i>				
Cons	132.6	–	106.8 to 158.4	0.000
Age	–0.8	–0.6	–1 to –0.5	0.000
LR	0.1	0.1	–0.1 to 0.3	0.463
BMI	–0.1	–0.1	–0.7 to 0.4	0.645
WC	0.2	0.2	–0.1 to 0.6	0.233
HOMA	–1.2	–0.2	–2.7 to 0.4	0.15
M.Eft	0	0	–1.5 to 1.6	0.965
<i>HRR3 (R² = 0.58; p = 0.0001)</i>				
Cons	109.7	–	82.6 to 136.9	0.000
Age	–0.7	–0.6	–1 to –0.4	0.000
LR	0.1	0.1	–0.1 to 0.4	0.213
BMI	–0.7	–0.3	–1.3 to –0.1	0.023
WC	0.5	0.4	0.1 to 0.9	0.011
HOMA	–1.3	–0.2	–3 to 0.4	0.126
M.Eft	–0.3	0	–2 to 1.3	0.693
<i>HRR4 (R² = 0.47; p = 0.007)</i>				
Cons	109.2	–	84.3 to 134	0.000
Age	–0.5	–0.4	–0.7 to –0.2	0.000
LR	0.2	0.2	0 to 0.4	0.095
BMI	–0.4	–0.2	–1 to 0.1	0.12
WC	0.2	0.1	–0.2 to 0.5	0.359
HOMA	–0.3	0	–1.8 to 1.3	0.741
M.Eft	0.2	0	–1.3 to 1.7	0.897
<i>HRR5 (R² = 0.50; p = 0.003)</i>				
Cons	106.7	–	80.7 to 132.8	0.000
Age	–0.6	–0.5	–0.8 to –0.3	0.000
LR	0.2	0.2	–0.1 to 0.4	0.131
BMI	–0.4	–0.2	–1 to 0.2	0.179
WC	0.1	0.1	–0.2 to 0.5	0.506
HOMA	–0.2	0	–1.9 to 1.4	0.766
M.Eft	1	0.1	–0.6 to 2.6	0.203

Cons = Constant; LR = lifetime risk; M.Eft = mean epicardial fat thickness.

ently healthy Korean adults reported that the waist-to-hip ratio and percentage of body fat mass were better indicators of low HRV measures than BMI [6]. Poliakova et al. [7] showed that age, WC, and percentage of fat presented an independent association with HRV, whereas BMI pre-

sented no association. These findings indicate that alterations in autonomic function not detected during rest might be observed following exercise. In addition, WC only predicted slower HRR at 3 min, not at 1 min, which is 1 min into recovery and preferred in most studies. This also could suggest that obesity-related autonomic dysfunction might be better evaluated during the second slow HRR decay phase. It has been suggested that early HRR indices (such as HRR at 1 min) could be considered as markers of cardiac parasympathetic outflow [22]. In contrast, the second slow heart rate decay phase was thought to be associated with the gradual withdrawal of sympathetic activity and with the clearance of stress system metabolites [22]. As such, obesity might initially affect only sympathetic activity, which might play an important role in the pathogenesis of obesity-associated ANS dysfunction [22].

In the present study there were no significant correlations between adiposity and the electrophysiological parameters such as SSR and RRIV obtained at rest, which might have been the large normal ranges for SSR and RRIV that were considered for analysis, or the lack of a control group. Furthermore, the patients were tested only once at the time of enrollment in the study; follow-up data were not obtained. Epicardial fat has significantly higher rates of lipolysis and lipogenesis than other types of visceral fat [18]. Given its anatomical proximity to the heart, epicardial fat interacts locally with the coronary arteries and the myocardium via paracrine or vasocrine pathways. The EFT is strongly correlated with visceral obesity, metabolic syndrome, diabetes mellitus, and cardiovascular disease [18, 23]. In this respect, a potential relationship between EFT and ANS dysfunction – if found in obesity independent of other risk factors – could explain increased mortality.

In the present study, there was not a relationship between EFT and ANS function, which could be due to the release of compartment-specific alterations in the balance of sympathetic/parasympathetic outflow; WC could contribute to ANS dysfunction to a greater degree than EFT. Increased parasympathetic dominance in the visceral compartment, and increased sympathetic tone in the thoracic and movement compartments could play a role in metabolic syndrome, including visceral fat accumulation [20, 24, 25]. The ANS innervates fat depots that are positively associated with catecholamine production by the ANS [26, 27]. The biologic mechanisms whereby visceral fat could contribute to ANS dysfunction might involve adipocytokines secreted by fat cells [28]. Another reason for the lack of observation of an association between EFT

and ANS function could be that EFT measurements are imperfect, representing only 1 planar dimension that is subject to probe angulation, adequate visualization of the cardiac structure, and the given phase of the cardiac cycle chosen to be measured. As such, EFT may not represent average fat thickness all around the heart and may not be accurate in its predictive value.

The present findings could have significant practical applications; if it can be definitively shown that central obesity is inversely related to ANS dysfunction in the hearts of obese individuals, such a relationship could be considered as an early marker of cardiovascular disturbance in this patient population. The long-term sequelae of ANS dysfunction that manifest as lower HRV are unknown, but might contribute to cardiovascular, lipid, and endocrine abnormalities, as these mechanisms are regulated by the ANS. Relevant evidence had been reported in studies that demonstrate associations between lower HRV and coronary artery disease, heart failure, hyperlipidemia, hypertension, and prediabetic and diabetic states [29, 30].

One limitation of the present study was the evaluation of HRR after exercise. While this might not be representative of long-term evaluation on 24-hour ECG monitoring, it does provide some important data concerning long-term variability and fluctuation. Other limitations were the small sample size, which was predominantly fe-

males, precluding a gender analysis, and measurement of EFT using echocardiography, which is less accurate than CT. Larger-scale studies that include obese patients and healthy controls are needed to confirm the present findings.

Conclusion

In this study, central adiposity (WC, but not EFT) was associated with ANS dysfunction; this relationship was observed primarily in terms of sympathetic activity. As such, we speculate that WC might be more strongly associated with ANS dysfunction than EFT, and might be an important mechanism in the pathogenesis of increased mortality in obesity. The second slow HRR decay phase might be more useful than early HRR indices for evaluating ANS function. Additional research targeting central adiposity for the prevention or attenuation of ANS dysfunction at an earlier stage in obese individuals may be warranted.

Disclosure Statement

The authors report no conflicts of interest.

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