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Obesity and heart rate variability in men with myocardial infarction

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Abstract

Background: *Obesity has been shown to affect heart rate variability (HRV). Adipokines (hormone-like peptides secreted by adipose tissue) display several bioactivities and have an impact on the cardiovascular system. The aim of the study was to evaluate the impact of obesity (BMI ≥ 30) and adipokines (leptin, adiponectin and resistin) on HRV.*

Methods: *In 43 obese and 38 non-obese males with acute myocardial infarction, plasma adipokines were determined. 24-hour Holter ECG with time and frequency domain HRV analysis was performed.*

Results: *Anthropometric measurements, leptin and resistin were significantly higher and adiponectin was lower in the obese than in the non-obese group. SDNN, SDANN, SDNN-i, rMSSD, p-NN50 and HF were reduced in obese patients, whereas LF/HF was higher. Waist circumference was a better correlate of HRV parameters than body mass index. Several associations between HRV parameters and adipokines were observed: between SDNN and leptin ($r = –0.32$; $p < 0.001$) and resistin ($r = –0.26$; $p < 0.05$); SDANN and leptin ($r = –0.26$; $p < 0.05$) and resistin ($r = –0.29$; $p < 0.001$); SDNN-i and resistin ($r = –0.40$; $p < 0.001$); LF and leptin ($r = 0.22$; $p < 0.05$); HF and resistin ($r = –0.22$; $p < 0.05$); LF/HF and leptin ($r = 0.46$; $p < 0.001$) and resistin ($r = 0.44$; $p < 0.001$).*

Conclusions: *Obesity is related to sympathovagal imbalance characterized by depressed parasympathetic tone and increased sympathetic activity. The relation between blood leptin and resistin concentration to the HRV parameters may indicate a possible link between adipokines and disturbances of the autonomic nervous system.* (Cardiol J 2008; 15: 43–49)

Key words: obesity, heart rate variability, myocardial infarction

Introduction

Heart rate variability (HRV) is a result of the influence of the autonomic nervous system on the heart. During the last two decades a decreased HRV has been recognized as a factor related to cardiovascular mortality, including sudden cardiac death [1, 2]. The time domain method of evaluating HRV is considered ideal for the analysis of long-term recordings and assessment of overall HRV [3].

Excess body fat not only promotes clusters for cardiovascular risk factors [4] but is an independent cardiovascular risk factor [5]. Obesity in patients with established coronary artery disease worsens the prognosis [6] and is associated with acute coronary syndromes [7]. It has been shown that obesity is related to disorders of the autonomic nervous system independently and due to coexisting diabetes,

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hyperinsulinemia, dyslipidemia and arterial hypertension [8–12].

Adipose tissue secretes adipokines — hormone-like peptides which have an impact on glucose and lipid metabolism, inflammatory process and other bioactivities [13]. Recently the role of the adipokines in HRV has attracted attention. Leptin, a strong correlate of the degree of obesity, stimulates the sympathetic nervous system [14, 15] and the relation between serum leptin levels and sympathetic activity independently of the amount of observed body fat was observed [16]. It has been suggested that increased plasma leptin concentration may be a result of the selective tissue resistance to its satiety and weight-reducing effect whereas the sympathoexcitatory action of leptin is preserved [17]. Low serum concentrations of adiponectin, an adipokine considered as a protective cardiovascular factor [18], was associated with sympathovagal balance favouring relative sympathetic activation in patients with type-2 diabetes [19]. Resistin, an adipokine potentially linked to atherogenesis [20], has not yet been demonstrated to be linked with the automatic nervous system.

At present, as the rates of obesity and its sequel are rising steadily due to the Western lifestyle [21], all the aspects of adverse effects of obesity on the cardiovascular system seem to be an important issue.

The aim of the study was to evaluate the impact of obesity and selected adipokines (leptin, adiponectin and resistin) on cardiac autonomic nervous activity in patients with first acute myocardial infarction (AMI).

Methods

Study population

From the population of patients with first AMI successfully treated with primary percutaneous coronary intervention (TIMI flow grade 3, residual stenosis < 30%), 43 obese males (BMI ≥ 30) aged up to 65 years were selected for the study group. The control group consisted of 38 non-obese males (BMI < 25).

Diagnosis of AMI was based on clinical symptoms, electrocardiographic signs and elevation of myocardial necrotic markers. Exclusion criteria were conditions that either made HRV analysis impossible or had a significant impact on HRV parameters: clinical instability (Killip III–IV class), atrial fibrillation, atrioventricular or bundle branch block, temporary or permanent stimulation, significant valvular heart disease or severe hypertension. Pharmacological treatment with aspirin, clopidogrel, statins, beta-blockers, inhibitors of angiotensin II, nitrates and diuretics did not significantly differ between the groups.

The study was approved by the Internal Ethics Committee of the Medical University of Łódź, and each patient gave informed consent.

Anthropometric measurements

Body mass index (BMI), calculated as the body weight divided by the square of the height (kg/m^2), was used as a marker of obesity. Weight and height were measured while the subjects were fasting. Patients were designated as obese when BMI exceeded 30 kg/m^2 and were considered non-obese when BMI was below 25 kg/m^2. Waist circumference was measured at the widest diameter between the xiphoid process of the sternum and the iliac crest.

Heart rate variability analysis

24-hour Holter ECG was performed in all patients on the third or fourth day after AMI. A three-lead digital ECG recorder with Oxford Holter analyzer was used. This allowed automatic and manual analysis of two orthogonal bipolar ECG leads (CM V5 and CM V6) with a mean duration of 22.8 ± 1.2 hours. Supraventricular and ventricular ectopic beats, as well as artefacts, were identified and manually eliminated from the analysis. According to the present standard [3] long-term time domain and frequency domain variables, 24-hour recordings were analyzed with a sampling rate of 292 Hz.

Time domain variables:

— SDNN — the standard deviation of all intervals between adjacent QRS complexes resulting from sinus node depolarization (NN), i.e. the square root of variance, reflects all the cyclic components responsible for variability in the period of recording and is considered as an estimate of overall HRV, encompassing vagal and sympathetic influences;
— SDANN — the standard deviation of the average NN intervals assesses long-term components that influence HRV, mainly the sympathetic output;
— SDNN index (SDNN-i) — the mean of the 5-minute standard deviations of NN intervals calculated over 24 hours measures the variability due to cycles shorter than five minutes and reflects parasympathetic activity;
— rMSSD — the root mean square of successive differences in NN intervals is considered as an estimate of short-term components of HRV, corresponding to parasympathetic activity;

— p-NN50 — the proportion derived by dividing NN50 (the number of interval differences of successive NN intervals greater than 50 ms) by the total number of NN intervals. This is a measure of parasympathetic activity.

Frequency domain variables:

— LF (0.04–0.15 Hz) — the low frequency range reflects the mixture of sympathetic and parasympathetic activation;
— HF (0.15–0.40 Hz) — the high frequency range gives a measure of vagal control;
— LF/HF — an index that provides an assessment of the symphatovagal balance.

LF and HF were transformed into natural logarithms (ln).

Laboratory measurements

Fasting blood samples for measurements of adipokines were taken on the day following admission, and plasma was frozen at –70° until analysis with a sandwich enzyme-linked immunosorbent assay (ELISA).

Echocardiographic examination

Echocardiographic study was performed on the second-third day after admission with a Sonos 5500 S3 probe. A harmonic option was used to enhance the visualization of the endocardium. Left ventricular ejection fraction was assessed at 4- and 2-chamber apical views with biplane Simpson's formula to evaluate left ventricular systolic function.

Statistical analysis

Continuous data are expressed as mean ± ± standard derivation (SD). Variables were log--transformed before statistical analysis, if necessary. Comparisons between groups were performed using the two-tailed, non-paired Student's *t*-test or Mann-Whitney test, as appropriate. Categorical variables are presented as number and percentage of patients, and comparisons between analyzed groups were analyzed with the χ^2 test. Associations between analyzed parameters were examined using Spearman's correlation coefficient. A p value of < 0.05 was considered statistically significant. Statistica software (version 5.0) was used for statistical analysis.

Results

The clinical characteristics of the study group are presented in Table 1. There was no significant difference in mean age, time since the onset of symptoms to admission, or localization of AMI and left ventricular ejection fraction between the study groups. The occurrence of most cardiovascular risk

Table 1. Clinical characteristics of the study groups.

	Obese (n = 43)	Non-obese (n = 38)	p
Age	54.06 ± 7.04	55.26 ± 6.62	NS
Interval between the chest pain and admission to hospital [h]	3.93 ± 2.25	4.52 ± 2.60	NS
Anterior myocardial infarction	18 (41.86%)	16 (42.11%)	NS
Ejection fraction (%)	57.21 ± 8.82	55.63 ± 8.52	NS
Body mass index [kg/m^2]	32.00 ± 1.78	23.63 ± 1.27	< 0.0001
Waist circumference [cm]	112.16 ± 7.83	88.08 ± 7.21	< 0.0001
Smoking	27 (62.79%)	24 (63.16%)	NS
Hypertension	26 (60.47%)	15 (40.47%)	NS
Systolic blood pressure	123.95 ± 10.50	119.73 ± 12.14	NS
Diastolic blood pressure	75.34 ± 6.93	73.42 ± 8.06	NS
Diabetes mellitus	13 (30.23%)	7 (18.42%)	NS
HDL-cholesterol < 40 mg/dL	17 (39.53%)	7 (18.42%)	< 0.05
Dyslipidemia	31 (70.09%)	23 (60.53%)	NS
Leptin [ng/mL]	44.50 ± 19.01	17.23 ± 14.42	< 0.0001
Resistin [ng/mL]	27.26 ± 11.49	15.99 ± 9.09	< 0.0001
Adiponectin [ng/mL]	7.09 ± 4.36	10.81 ± 6.52	< 0.01

Table 2. Parameters of heart rate variability in the groups of obese and non-obese patients.

	Obese (n = 43)	Non-obese (n = 38)	p
SDNN	104.16 ± 26.81	119.49 ± 28.62	< 0.05
SDANN	87.60 ± 23.47	99.05 ± 27.62	< 0.05
SDNN-i	54.57 ± 27.06	67.36 ± 28.10	< 0.05
r-MSSD	33.80 ± 15.16	41.29 ± 16.27	< 0.05
p-NN50	5.36 ± 4.66	7.68 ± 5.25	< 0.05
LF ln	6.34 ± 0.63	6.41 ± 0.62	NS
HF ln	5.24 ± 0.63	5.59 ± 0.53	< 0.01
LF/HF	1.22 ± 0.08	1.15 ± 0.08	< 0.01

factors (hypertension, diabetes, smoking, dyslipidemia) was similar in both groups. A significant difference was observed only in the proportion of patients with high-density lipoprotein cholesterol (HDL-CH) < 40 mg/dL. The assessed anthropometric measurements (BMI and waist circumference), as well as mean blood leptin and resistin concentration, were significantly higher and mean adiponectin concentration was significantly lower in obese than in non-obese group (Table 1).

As shown in Table 2, significantly lower values of overall HRV expressed as lower SDNN were observed in obese subjects. This was due to the reduction in both long-term HRV (SDANN) and short-term HRV (SDNN-i). Moreover, lower values of other parameters reflecting parasympathetic tone (rMSSD, p-NN50, HF) were observed in obese patients. Higher values of LF/HF in obese patients indicated the advantage of sympathetic over parasympathetic activation in these subjects.

There were more HRV correlates for waist circumference (SDNN, SDANN, SDNN-i, rMSSD, HF and LF/HF) than for BMI (SDNN, SDNN-i and LF/HF). Mean blood leptin and resistin concentration were negatively related to SDNN and positively related to LF/HF. Leptin affected parameters that chiefly reflect the sympathetic output (SDANN and LF), whereas resistin affected parameters of both sympathetic and parasympathetic activity (SDANN, SDNN-i and HF). No significant association between adiponectin and parameters of HRV was revealed (Table 3).

Discussion

In patients surviving an AMI, the association between depressed HRV and an increase in the risk of death, mainly arrhythmic, has been widely elucidated in small studies and larger randomized studies [1, 2]. Obesity in patients with coronary artery disease worsens the prognosis [6] and its impact on the autonomic nervous system could be one of the possible ways of this deleterious action.

Several authors have observed that obesity and weight loss affect HRV [9, 22–25]. However, others [8, 26, 27] have detected no association between HRV and BMI. It has been documented with various methods in experimental [28] and clinical studies [9, 29–31] that parasympathetic activity is decreased in obesity. Our results seem to confirm that observation as there were significantly lower SDNN-i, MSSD, p-NN50 and HF in obese than in control subjects. Moreover, we demonstrated a negative correlation between anthropometric measurements (especially waist circumference) and the parameters reflecting parasympathetic activity. Disparate results come from the study by Kim et al. [8] who revealed a negative relation between r-MSSD and waist to hip ratio ($r = -0.38$; $p<0.05$).

Although high blood leptin concentration is often accompanied by sympathetic activation, studies on the norepinephrine kinetics assessed with the use of [3H]-labelled norepinephrine and analysis of the regional oxygen consumption revealed that regional sympathetic nervous system activity is heterogeneous in the obese state, and it was suggested that sympathetic activation spares the sympathetic nerves directed to the heart [32]. However,

Table 3. Correlation between parameters of heart rate variability and anthropometric measurements and adipokines.

	SDNN	SDANN	SDNN-i	rMSSD	p-NN50	LF	HF	LF/HF
Body mass index	–0.23***	–0.17	–0.29**	–0.16	–0.06	0.10	–0.20	0.29*
Waist circumference	–0.30**	–0.26***	–0.40*	–0.24***	–0.17	0.03	–0.32*	0.46*
Leptin	–0.32*	–0.26***	–0.19	–0.17	–0.02	0.22***	–0.14	0.46*
Resistin	–0.26***	–0.29*	–0.40*	–0.15	–0.12	0.07	–0.22***	0.44*
Adiponectin	0.06	0.10	0.16	0.16	0.01	–0.07	0.05	–0.14

*p < 0.001; **p < 0.01; ***p < 0.05

the results of the present study show sympathetic overactivity in obesity as reflected by significantly lower SDANN in obese than in lean subjects, and the negative relation between SDANN and waist circumference, leptin and resistin. This result is consistent with Rabbia et al. [24] who observed the tendency for lower values of SDANN in obese patients. Moreover, Karason et al. [23] and Naut et al. [24] have shown the increment in SDANN after weight-loss. During sympathetic activation and in conditions known for increased circulating catecholamines such as heart failure and aging LF power has been identified as a parameter reflecting mainly sympathetic activity, whereas in stable conditions it reflects a fusion of parasympathetic and sympathetic impact [33]. No significant difference in LF between obese and non-obese patients was observed in our study and in the study of Rabbia et al. [22]. However, in agreement with Paolisso et al. [16] plasma leptin concentration is positively associated with LF. Disparate results were revealed by Kim et al. [8] who showed a negative correlation between LF and waist to hip ratio.

In agreement with previous reports [9, 10, 16] we observed a shift in the sympathovagal balance toward an increase in sympathetic activation expressed as an increased LF/HF in obese patients. We also noted the positive association between plasma leptin and resistin concentration and LF/HF.

In our study, adiponectin was not related to any HRV variables. Information from other studies conducted in groups of patients with type-2 diabetes, suggests that there are possible links between hypoadiponectinemia and cardiac sympathetic activity. Wakabayashi et al. [34] showed an independent negative association between blood adiponectin concentration and 24-hour LF/HF ratio. In the study by Takahashi et al. [35], adiponectin did not correlate with HF power or LF/HF, but cardiac scintigraphy with radioactive-labelled metaiodobenzylguanidine (^{123}I-MIBG — an analogue of guanethidine which accumulates in norepinephrine storage granules in postganglionary sympathetic neurons) showed that in type-2 diabetes, low blood adiponectin concentration was associated with sympathetic activation. The authors revealed that in patients with hypoadiponectinemia there is a lower delayed myocardial uptake and higher washout rate of ^{123}I-MIBG.

We have not come across any paper concerning the relationship between resistin and HRV parameters; however, in our group of patients these associations were similar to those concerning leptin, i.e. resistin was negatively associated with SDNN, SDANN, SDNN-i and HF and positively associated with LF/HF. Attempts to explain these results led us to the studies on hyperresistinemia, presumably induced by cytokines [36], interaction between inflammatory and autonomic systems [37–39] and, in the end, to a possible link between resistin, inflammation and sympathetic activation. The HRV correlates of resistin presented in this study are similar to the correlates of C-ractive protein in other studies [39, 40]. This observation is coherent with the previously reported association between blood resistin and C-ractive protein concentration [41, 42].

A limitation of our study is that in each patient a different cluster of the possible cofactors might have an impact on cardiac autonomic control. It has been shown that lower HRV is observed in metabolic disorders (hypertension, type-2 diabetes and dyslipidemia) especially when clustering [43], and it is very unusual for the obese individual to be free from any of these problems. Although the medication was almost identical in the whole study group, the applied doses differed in individual patients, and might have affected our results.

This study was performed exclusively on men, so the results cannot be generalized for the whole population. The gender-related differences in fat distribution, namely the presence of more abundant subcutaneous fat in women and of visceral fat in men, that have an impact on cardiovascular risk profile [44] may influence the mode of HRV modulation.

Conclusion

Obesity is related to sympathovagal imbalance characterized by depressed parasympathetic tone and increased sympathetic activity. The relation between blood leptin and resistin concentration to the HRV parameters may indicate a possible link between adipokines and disturbances of the autonomic nervous system.

Future investigations on larger groups of patients, with HRV response to stimuli, complex evaluation of automatic nervous system including baroreceptor reactivity as well as prospective study with follow-up observation are warranted to thoroughly elucidate the impact and mechanism of adverse effects of obesity on cardiac function.

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