Obesity and heart rate variability in men with myocardial infarction

Katarzyna Piestrzeniewicz, Katarzyna Łuczak, Małgorzata Lelonek, Jerzy Krzysztof Wranicz and Jan Henryk Goch

1st Department of Cardiology, Medical University of Łódź, Poland

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,
hyperinsulinemia, dyslipidemia and arterial hyper-
tension [8–12].

Adipose tissue secretes adipokines — hor-
mone-like peptides which have an impact on glu-
cose 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, stimu-
lates the sympathetic nervous system [14, 15] and
the relation between serum leptin levels and sym-
pathetic activity independently of the amount of
observed body fat was observed [16]. It has been
suggested that increased plasma leptin concentra-
tion may be a result of the selective tissue resist-
ance to its satiety and weight-reducing effect
whereas the sympathoexcitatory action of leptin is
preserved [17]. Low serum concentrations of adi-
ponectin, an adipokine considered as a protective
cardiovascular factor [18], was associated with sym-
pathovagal balance favouring relative sympathetic
activation in patients with type-2 diabetes [19].
Resistin, an adipokine potentially linked to athero-
genesis [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
vascular system seem to be an important issue.

The aim of the study was to evaluate the im-
 pact of obesity and selected adipokines (leptin, adi-
ponectin and resistin) on cardiac autonomic nerv-
ous 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 symp-
toms, 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 pa-
rameters: clinical instability (Killip III–IV class),
atrival fibrillation, atrioventricular or bundle branch
block, temporary or permanent stimulation, signifi-
cant 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 be-
tween 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/m²),
was used as a marker of obesity. Weight and height
were measured while the subjects were fasting. Pa-
tients were designated as obese when BMI exceeded
30 kg/m² and were considered non-obese when BMI
was below 25 kg/m². 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 pa-
tients on the third or fourth day after AMI. A
three-lead digital ECG recorder with Oxford Hol-
ter 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. Accord-
ning 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 es-
timate of overall HRV, encompassing vagal and
sympathetic influences;

— SDANN — the standard deviation of the aver-
age NN intervals assesses long-term compo-
nents that influence HRV, mainly the sympa-
thetic output;

— SDNN index (SDNN-i) — the
mean of the
5-minute standard deviations of NN intervals
measures the varia-
tility 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 sympathovagal 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 χ² 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>
<thead>
<tr>
<th>Table 1. Clinical characteristics of the study groups.</th>
</tr>
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<tbody>
<tr>
<td>Obese</td>
</tr>
<tr>
<td>(n = 43)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Interval between the chest pain and admission to hospital [h]</td>
</tr>
<tr>
<td>Anterior myocardial infarction</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
</tr>
<tr>
<td>Body mass index [kg/m²]</td>
</tr>
<tr>
<td>Waist circumference [cm]</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>HDL-cholesterol &lt; 40 mg/dL</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Leptin [ng/mL]</td>
</tr>
<tr>
<td>Resistin [ng/mL]</td>
</tr>
<tr>
<td>Adiponectin [ng/mL]</td>
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</tbody>
</table>
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Table 2. Parameters of heart rate variability in the groups of obese and non-obese patients.

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

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).

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

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

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

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,
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 hyperadiponectinemia 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 postganglionic sympathetic neurons) showed that in type-2 diabetes, low blood adiponectin concentration was associated with sympathetic activation. The authors revealed that in patients with hyperadiponectinemia 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-reactive protein in other studies [39, 40]. This observation is coherent with the previously reported association between blood resistin and C-reactive 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.

**Acknowledgements**

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References


34. Wakabayashi S, Aso Y. Adiponectin concentrations in sera from patients with type 2 diabetes are negatively associated with sympathovagal balance as evaluated by power spectral analysis of heart rate variability. Diabetes Care, 2004; 27: 2392–2397.


