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OVERWEIGHT, DYSLIPOPROTEINEMIA, AND HEART RATE VARIABILITY MEASURES

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SUMMARY
Chronic stress could be a risk factor triggering, aggravating or causing overweight, dyslipoproteinemia and coronary artery disease.

OBJECTIVE: The purpose of this study was to determine the association between stress assessed by heart rate variability measures, dyslipoproteinemia, and overweight.

METHODS: Total cholesterol, high and low density lipoproteins cholesterol and triglycerides were analyzed by enzyme methods; heart rate variability was evaluated using a computer program for analysis of cardiointervals in 47 individuals with dyslipoproteinemia.

RESULTS: Positive correlations were found between heart rate and low density lipoprotein cholesterol, between mental stress and total cholesterol/high density lipoprotein cholesterol, between physical stress and total cholesterol, low density lipoproteins cholesterol, triglycerides and body mass index, and between functional age and health risk, and total cholesterol and low density lipoprotein cholesterol. The total cholesterol and low density lipoprotein cholesterol were negatively correlated with the time- and frequency-domain heart rate variability measures. A chronically increased health risk (> 65%) was observed in 15 individuals with dyslipoproteinemia, 11 of them with body mass index exceeding 25.0 kg/m².

CONCLUSION: Heart rate variability measures decrease in individuals with dyslipoproteinemia. Decreasing of heart rate variability is induced by the increased activity of the sympathetic branch of the autonomic nervous system under chronic stress effect. Results of our study revealed a significant association between physical stress, serum lipids and overweight and risk of coronary artery disease.

Key words: dyslipoproteinemia, overweight, heart rate variability, stress, health risk

ABBREVIATIONS:
DLP = dyslipoproteinemia;
CAD = coronary artery disease;
HRV = heart rate variability;
TC = total cholesterol;
HDL-C = high density lipoprotein cholesterol;
LDL-C = low density lipoprotein cholesterol;
TG = triglycerides;
BMI = body mass index;
X = mean value of successive cardiointervals;
STV = short-term variability;
LTV = long-term variability;
TDI = time-domain index;
AMo = amplitude of the mode;
Plw = spectral power of cardiointervals (R-R) in the low-frequency area;
Pmw = spectral power of cardiointervals (R-R) in the medium-frequency area;
Psw = spectral power of cardiointervals (R-R) in the high-frequency area;
FDI = frequency-domain index (ratio of the spectral powers of R-R in the low to high frequency area);
PS = physical stress;
MS = mental stress;
FA = functional age;
HR = health risk.

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INTRODUCTION
The prevalence of obesity is high and increasing in the present conditions of intensifying urbanization, reduced physical activity and high level of stress factors in the occupational and living environment. In Bulgaria it is estimated to be in the range from 3 - 11% in early childhood to 20 - 36% in adult age\textsuperscript{1,2}. The high prevalence of these stressors increases the risk of chronic non-communicable diseases. The relationship between mental stress and metabolic activity and its effect on the cardiovascular system is a current health problem. There is evidence that certain major cardiovascular risk factors are stimulated by stress effects\textsuperscript{3,4}. The psychological stress can interact with cardiovascular risk factors and the physiological reactivity, tonically increased towards ergotropic response, can increase in its turn the risk of clinical manifestations of coronary artery disease (CAD)\textsuperscript{5-7}. Heart rate variability (HRV) measures are a physiological indicator and marker of the hazardous effect of stress factors on human organism. These measures are estimated by the HRV analysis; they are function of the balance between the activity of the sym-
pathetic and parasympathetic branches of the autonomic nervous system. The objective of the present study was to determine the association between stress evaluated with HRV measures, the indices of lipid metabolism and overweight, and the health risk.

**METHODS**

The study included 47 individuals (18 men, 29 women, mean age 52.7 yrs) with dyslipoproteinemia without clinically manifested CAD. We assessed the HRV measured in sitting and lying position, the lipid status and body mass index. The study was conducted in accordance with the Declaration of Helsinki [Br Med J 1964;ii:177].

The HRV analysis was performed using a computerized test system for registration, collection and analysis of cardiointervals (STRESS-test)6,9.

The following HRV measures were analyzed: time-domain measures: X (msec), mean value of successive cardiointervals (R-R), respectively mean heart rate, short-term variability (STV, msec), long-term variability (LTV, msec), time-domain index (TDI), amplitude of the mode (AMo (yr%)); frequency-domain measures: spectral power of R-R in the low-frequency band 0.00-0.05 Hz (Plw) (sec²/Hz), R-R power in the medium frequency band 0.05-0.15 Hz (Pmw) (sec²/Hz), spectral power of R-R in the high frequency band 0.2-0.4 Hz (Psw) (sec²/Hz), frequency-domain index which is a ratio of R-R spectral power in the low frequency band to R-R spectral power in the high frequency band (FDI) (arb. units); HRV indices: physical stress (PS) (arb. units), mental stress (MS) (arb. units), functional age (FA) (yr), and health risk (HR, %).

The lipid indices were studied using the following methods:

Total cholesterol (TC) - CHOD-PAP enzymatic colorimetric method with kit produced by “Human”, Germany10, triglycerides (TG) - enzyme colorimetric GPO-PAP method by “Human”11, high density lipoproteins cholesterol (HDL-C) - precipitation with 20% w/v polyethylene glycol in glycine buffer, pH = 10 with kit produced by “Sentinel”, Italy; low density lipoproteins cholesterol (LDL-C) - calculated by Friedewald's formula (TC - HDL-C) - TG/2.212. Three subjects with TG > 4.5 mmol/L were tested by a direct determination of LDL-C with kit by “Human”, Germany. The BMI was calculated from the ratio of weight (kg) and the squared height (m²). The results were processed statistically using multiple correlation and multiple stepwise regression analysis.

**RESULTS**

The correlation analysis revealed the following relationships between lipid indices and HRV measures (Table 1).

Mean heart rate correlated positively with LDL-C (r = 0.322*). There was a negative correlation of time- and frequency-domain HRV measures with TC and LDL-C. Mental stress correlated significantly with the TC/HDL-C index, and physical stress - with TC, LDL-C, TG and BMI. BMI showed positive correlations with TC (r = 0.654**), LDL-C (r = 0.637**) and the TC/HDL-C index (r = 0.462**). TG in 19 (40%) individuals was > 2.2 mmol/L. BMI of 23 individuals varied from 18.5 to 29.5. 18 individuals had BMI within the range of 25 - 29.9, and 6 individuals had BMI > 29.9. Chronically increased health risk > 65% was found for 15 (32%) of individuals with DLP and 11 (73%) of them had BMI exceeding 25.0. These individuals showed significant correlation between PS and BMI (r = 0.566). The individuals with HR < 65% revealed significant correlation between PS and HR (r = 0.774) and between MS, HR and BMI (r = 0.525 and r = 0.479, respectively).

Multiple stepwise regression analysis was used to determine whether the lipid indices and BMI had any predictive value for the changes in HRV

**Table 1.** Significant correlations between lipid metabolism indices and HRV measures

<table>
<thead>
<tr>
<th>Indices</th>
<th>TC</th>
<th>LDL-C</th>
<th>TG</th>
<th>TC/HDL-C</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-domain measures:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>r = 0.322*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STV</td>
<td>r = 0.317*</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>LTV</td>
<td>r = 0.375**</td>
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<tr>
<td>TDI</td>
<td>r = 0.308*</td>
<td></td>
<td></td>
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<tr>
<td>Frequency-domain measures:</td>
<td></td>
<td></td>
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<tr>
<td>Plw</td>
<td></td>
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<tr>
<td>Pmw</td>
<td>r = 0.398**</td>
<td>r = 0.438**</td>
<td></td>
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<tr>
<td>Psw</td>
<td>r = 0.438**</td>
<td>r = 0.402**</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HRV measures:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MS</td>
<td>r = 0.308*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>r = 0.472**</td>
<td>r = 0.531***</td>
<td>r = 0.442**</td>
<td>r = 0.560***</td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>r = 0.452**</td>
<td>r = 0.452**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>r = 0.438**</td>
<td>r = 0.387**</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Rt = 0.29, * p < 0.05; Rt = 0.37, ** p < 0.01; Rt = 0.50.
measures just as the physical indicators of stress do. The results are presented in Table 2. It was found that TC and BMI had a statistically significant and predictive value for the changes in PS; TC and TG were predictors of FA; TC was a predictor of Health Risk.

DISCUSSION

Chronic stress could induce a shift of the autonomic balance towards increased activity of the sympathetic function. This causes a decrease of heart rate variability, which is considered a significant risk factor for CAD development, and leads to a greater potential health risk. The major biomarker of the stress effect is the chronic increase of activation in the sympathetic branch of the autonomic nervous system, i.e. sympathicotonia prevails even in complete rest, a finding suggested by the bioconstants investigated in the present study.

Correlations between R-R variability and the lipid indices were most likely due to the prolonged chronic stress effect. This exposure modifies the autonomic cardiovascular regulation assessed by HRV measures and the lipid status as evidenced by other authors. Stress is considered to be also a cause for obesity. The correlations between Physical Stress and lipids on the one hand and Physical Stress and BMI on the other are most probably an expression of the low physical activity of the studied persons. The established predictive value of lipid indicators TC and TG, and of BMI in relation to physical stress and functional age shows that stress can predispose to a development of CAD. The results of our study suggest also that HRV analysis can provide significant information about the metabolic activity, i.e. HRV indicators can be used to assess the metabolic balance. The fact that 32% of the studied subjects with DLP have elevated HR, determined by HRV measures, and 73% of them are overweight, underlines the role of overweight as a risk factor and its relation to chronic stress.

The results of this study show that HRV in DLP individuals is altered as a result of the increased sympathetic tonus of the autonomic nervous system under chronic stress. Significant correlation and related increased risk from CAD exists between physical stress, changes in lipid indices and overweight. These data can be used in a prospective surveillance of patients with increased health risk and could be the basis for an enhanced study covering other risk factors.

REFERENCES

11. Megrow R, Dunn D, Biggs HG. Manual and continu-
OVERWEIGHT, DYSLIPOPROTEINEMIA, AND HEART RATE VARIABILITY MEASURES


ИЗБЫТОЧНЫЙ ВЕС, ДИСЛИПОПРОТЕИНЕМИЯ И ПОКАЗАТЕЛИ СЕРДЕЧНОЙ ВАРИАТИВНОСТИ

Н. Дончева, Р. Николова, С. Данев

РЕЗЮМЕ
Хронический стресс может быть отключающим, усугубляющим или причинным фактором риска избыточного веса, дислипопротеинемии и болезни коронарных сосудов.

Цель: Работа ставит себе цель установить существует ли связь между стрессом и показателями сердечной вариативности, дислипопротеинемии и избыточного веса.

Методы: ОХ, ЛВП-Хол, ЛНП-Хол и триглицериды исследованы с помощью энзимных методов, а сердечная вариативность посредством применения компьютерного метода регистрации сердечных интервалов у 47 больных с дислипопротеинемией.

Результаты: Обнаружены положительные корреляции между:
- сердечной частотой и Хол – ЛНП;
- индексами нервно-психического стресса и ОХ/Хол-ЛВП;
- индексом физического стресса и ОХ, Хол-ЛНП, триглицеридами и индексом массы тела;
- индексами оценки функционального возраста и риска здоровья у ОХ, Хол-ЛНП.

ОХ и Хол-ЛНП отрицательно коррелируют с показателям времени и частотно-базированными показателями сердечной вариативности. Хронически повышенный риск здоровья (>65%) наблюдается у 15 больных с дислипопротеинемией, при чем у 11 из них индекс массы тела свыше 25.0.

Заключение: Сердечная вариативность снижена у больных с дислипопротеинемией в результате повышенной тонической активности симпатико-васкулярной части вегетативной нервной системы, по всей вероятности под воздействием хронического стресса. Между физическим стрессом, липидами и избыточной массой тела существует достоверная зависимость и связанный с этим риск коронарной болезни.