

RELATIONSHIP BETWEEN HEART RATE VARIABILITY AND HYPERCHOLESTEROLAEMIA

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SUMMARY

A statistically significant correlation between chronic (tonic) distress (expressed by long-term depression of heart rate variability - HRV) and the increase of the serum lipid level was found in the experimental group (39 clinically healthy subjects with hypercholesterolaemia; 16 women and 23 men; mean age 42.4 ± 2.45 years). A statistically significant relationship was found also between the experimental and control group (39 healthy normocholesterolaemic subjects; 18 women and 21 men; mean age 43.7 ± 2.18 years) when comparing distress indicating HRV-based measurements. Significant predictors of HRV depression were: total cholesterol and low-density lipoprotein cholesterol.

The effect of a 3-month special diet served to 17 subjects selected from the experimental group led to a decrease of serum lipids but did not influence substantially HRV parameters. It can be concluded that HRV parameters reflecting stress reaction correlate with atherogenic serum lipids; their separate follow-up (which is quicker, easier and cheaper) can be used for prediction of cardiovascular health risk and probably for disorders in serum lipid metabolism.

Key words: chronic distress, serum lipids, heart rate variability.

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INTRODUCTION

The relationship between tonic, vagal-sympathetic ratio [assessed by heart rate variability (HRV)] and lipid metabolism was not studied sufficiently till now. It was found (10) that dietetic regimes resulting in a decreased body weight caused an increase of parasympathetic tonus (assessed by HRV analysis). It was also found, that hypercholesterolaemia does not alter autonomic cardiovascular regulation (assessed by HRV, blood pressure variability and baroreflex sensitivity) (15). In a recent study (5), we found, that increased serum lipid level correlates significantly with a chronically increased sympathetic tone. As an unfavourable drift in HRV and serum lipids contribute substantially to the development of cardiovascular pathology, it is important to reveal their mutual relationship: if there is any correlation, which of them play the major role. Many recent reports confirm that elevated serum total cholesterol and LDL-C levels are factors contributing to the development of coronary heart disease (CHD) (2, 6-8, 12, 13, 20, 27, 28, 31). Disorders of lipid metabolism increase the cardiovascular health hazard for CHD by facilitating the endothelial injury of the vascular wall and the proliferation of vascular smooth muscle cells (1-3, 17, 29). The pathophysiological mechanism includes an alteration of the permeability of the cell membrane to lipoproteins which permits the influx of low density lipoprotein cholesterol (LDL-C) into the intima of the artery and the consequent process of atherosclerotic plaque development.

According to the Framingham Heart Study in persons free of clinically apparent heart disease the reduced heart rate variability also contributed to the increased risk for subsequent cardiac events (30). Computer analysis of HRV offered substantial prognostic information beyond that provided by the evaluation of traditional cardiovascular risk factors.

Heart rate variability has a considerable potential to provide insight in the role of autonomic nervous system fluctuations for the development of cardiovascular disorders in normal healthy individuals as well as in patients (26). Decreased variability of R-R intervals are a valuable predictor of mortality in various clinical populations (11, 14, 24, 25). Decreased HRV predicted both death and arrhythmic events with greater sensitivity and specificity than conventional predictors such as the left ventricular ejection fraction. Decreased HRV is also a powerful risk stratifier for overall mortality, induced and spontaneous ventricular tachycardia, and sudden death following myocardial infarction (16). Heart rate variability is successfully used in many different branches of psychophysiological and clinical medicine (16, 18, 19, 23).

Our experience shows that HRV has a predictive value for the development of essential hypertension and coronary heart disease (CHD). We found also, that the chronic (tonic) increase of sympathetic tonus is the main physiological correlate of overstress or s. c. distress.

As the relationship between the tonic distress (reflected by HRV) and the level of serum lipids is not completely clear, the aim of this study was to determine it by following up

List of acronyms used

HRV - Heart Rate Variability, VE - Vegetative Equilibrium, HS - Homeostasis, TP - Total Spectral Power, FA - Functional Age, CI - Classification Index, TC - Total Cholesterol, HDL-C - High-Density Lipoprotein Cholesterol, LDL-C - Low-Density Lipoprotein Cholesterol, TG - Triacylglycerols, PSC - Psycho-somatic Complaints, R-R - Cardiointervals

those factors in selected experimental group as well as in controls.

MATERIAL AND METHODS

Subjects

A. Experimental group consisting of 39 clinically healthy subjects (16 women and 23 men, mean age 42.4 ± 2.45 years) with elevated serum total cholesterol as well as elevated triacylglycerol levels or both (hypercholesterolaemia group).

B. Age-matched control group consisting of 39 healthy normocholesterolaemic subjects (18 women and 21 men with mean age 43.7 ± 2.18 years).

Methods

All subjects had a complete physical examination and a medical history with no cardiovascular disease or medication.

The following parameters were recorded: heart rate variability, serum lipids, psychosomatic complaints and arterial blood pressure.

Heart rate variability was registered at 10 min rest in a sitting position between 9.0 a.m. and 10.0 a.m. on three consecutive days. The obtained indices reflect time domain as well as frequency domain-based measures of HRV: vegetative equilibrium (VE), reflecting the present autonomic balance; homeostasis (HS), reflecting the quality of adaptation to the demands of everyday life by means of the amount of heterostatic drift; total spectral power (TP), reflecting the spontaneous oscillations in the activity of respiratory, cardiovascular and thermoregulatory brain centres; functional age (FA), based on age-related values of HRV measures and classification index (CI), unifying all those measures multiplied by their weight coefficients according to the results of singular values of decomposition method for deriving main components (4).

The lipid metabolism was investigated on the first day, before HRV measurement, by means of the following analyses: enzymatic test GPO-PAP, Merck, Darmstadt for serum triacylglycerol levels (TG, mmol/l); colorimetric test Lachema, Brno, Czech Republic for serum total cholesterol levels (TC, mmol/l); test of Lachema, after previous precipitation with magnesium dichloride and dextran sulphate for serum high-density lipoprotein cholesterol levels (HDL-C, mmol/l); Friedewald's formula (9) was used for calculation of serum low-density lipoprotein cholesterol levels (LDL-C, mmol/l) from serum total cholesterol, triacylglycerols and HDL-C.

Subjective assessment of psychosomatic complaints (PSC) was performed by Danev's questionnaire based on 22 questions focused on physiological, psychological and behavioral disorders, and is expressed in per cent (4).

Arterial blood pressure was measured before and after testing sessions: systolic (RRs) and diastolic (RRd).

ANOVA, Student-Fisher t-test, multiple correlation analysis, multiple stepwise regression analysis, linear and non-linear regression analyses were used.

RESULTS

The mean group values of the obtained results of the persons in both groups are presented in Table 1 as well as the normal (for serum lipids) and the age-related (for HRV)

Table 1. Measured and normal (resp. age-related values) of serum lipids and HRV parameters, in experimental and control groups

Parameters	1 Normal (age-related) values	2 Experimental group N = 39, mean age 43.7 ± 2.18 $\bar{X} \pm S\bar{X}$	3 Control group N = 39, mean age 42.4 ± 2.45 $\bar{X} \pm S\bar{X}$	t-test p (2 - 3)
1. TC (mmol/l)	5.20	7.30 ± 0.23	5.07 ± 0.15	< 0.01
2. HDL-C (mmol/l)	1.20	1.55 ± 0.07	0.91 ± 0.05	< 0.05
3. LDL-C (mmol/l)	3.40	5.01 ± 0.28	3.39 ± 0.13	< 0.01
4. TG (mmol/l)	2.00	3.23 ± 0.93	1.55 ± 0.14	< 0.05
5. VE (s^{-1})	1.03	2.19 ± 0.23	0.95 ± 0.13	< 0.05
6. HS (%)	1.84	0.58 ± 0.16	1.94 ± 0.25	< 0.05
7. TP (s/Hz^2)	6.48	4.98 ± 1.63	7.43 ± 1.55	< 0.01
8. CI (arb. un.)	0.00	-30.56 ± 5.17	-7.83 ± 1.24	< 0.01
9. FA (years)	-	49.70 ± 4.03	43.80 ± 3.39	< 0.01
10. RRs (mm Hg)	120	149.0 ± 24.0	131.0 ± 28.0	< 0.05
11. RRd (mm Hg)	80	92.0 ± 18.0	78.0 ± 24.0	ns
12. PSC (%)	-	54.2 ± 14.3	26.15 ± 7.08	< 0.01

\bar{X} - group mean value; $S\bar{X}$ - standard error

values. Comparison between experimental and control groups reveals that all serum lipids and HRV data differ statistically significantly. On this basis it is possible to conclude that the experimental group as a whole is exposed to a higher level of cardiovascular health risk as compared with the control group.

Multiple correlation analysis was used to reveal the statistical relationships between groups. The thirty pairs of significant and highly significant relationships between four groups of investigated parameters which were found to show that some of the HRV parameters are interdependent, and that the activity of cardiovascular brain centres, responsible for HRV drift, reflects in some way the disturbance in lipid metabolism (or vice versa).

This is evident from the calculated correlation coefficients: a significance of $p < 0.05$ was found to exist between systolic blood pressure and psychosomatic complaints (PSC) ($r = 0.23$); VE and PSC ($r = 0.24$); TP and PSC ($r = 0.28$); TP and LDL-C ($r = 0.23$); FA and TC ($r = 0.26$); CI and TC ($r = 0.22$). A significance of $p < 0.01$ was found to exist between VE and LDL-C ($r = 0.22$); CI and PSC ($r = 0.26$); FA and LDL-C ($r = 0.32$) and CI and LDL-C ($r = 0.36$).

To determine which of the serum lipids (independent variables) are predictors of heart rate variability (dependent variable), linear regression and multiple stepwise regression analyses were employed. The obtained results are shown in Table 2, part A and B. It can be seen that the serum LDL-C levels are a significant predictor of homeostasis as well as of total spectral power. Both serum TC and LDL-C levels are significant predictors of CI.

Finally, all data were submitted to a non-linear regression analysis (exponential function: $y = e^{A * e^{BX}}$) in order to establish the regression models of VE, TP, FA and CI in relation to TC and LDL-C (Table 2, part C). The table presents the obtained predictive values of TC and HDL-C in relation to HRV parameters. The regression equations

Table 2. Regression analysis revealing the relationship between serum lipids and HRV measures in experimental group

A. Linear regression analysis of HRV parameters and LDL-C				
Dependent variable (y)	Independent variable (x)	Coefficient	t-value	F-ratio
HS	LDL-C	0.12	2.85*	11.86***
	Intercept	3.56	8.89***	
TP	LDL-C	0.49	3.39*	34.39***
	Intercept	18.05	8.25***	
B. Multiple stepwise regression analysis of CI dependence on serum lipids				
Dependent variable (y)	Independent variable (x)	Coefficient	t-value	F-ratio
CI	Intercept	-138.01	-2.74**	3.25*
	TC	5.26	1.95*	
	LDL-C	16.83	2.49**	
C. Regression models (parameters of exponential function equation: $y = e^a \cdot e^{bx}$) of HRV parameters and serum lipids				
Dependent variable (y)	Independent variable (x)	Coefficient	t-value	F-ratio
VE	Intercept	-94.73	-1.89*	4.01*
	LDL-C	0.12	1.57*/0.25**	
TP	Intercept	0.30	0.87*	4.10*
	LDL-C	0.11	1.67*/0.26*	
FA	Intercept	1.31	4.08*	7.50**
	LDL-C	0.08	2.33*/0.36**	
FA	Intercept	4.06	24.03*	4.85*
	TC	0.06	1.67*/0.26*	
CI	Intercept	4.12	15.64*	4.06*
	TC	9.58	1.37*/0.22*	
CI	Intercept	-95.99	-1.96*	6.89*
	LDL-C	9.49	2.31*/0.36**	

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

describe with satisfactory adequacy [according to the applied criteria: significance of the correlation coefficient (r), t-value for A-intercept and B-coefficient, and F-ratio], the dependence of each HRV parameter as a variable of serum TC and LDL-C as independent variables.

To obtain more knowledge on the question which of the cardiovascular health risk factors: serum lipids or HRV measures play the primary role, the influence of a specialized diet was followed up. The diet was administered for 3 months and included restricted intake of animal fat and a daily intake of cholesterol below 300 mg. Only seventeen subjects selected from the experimental group (8 men and 9 women, mean age 44.2 ± 2.24) were given the diet and were investigated by the same methodological approach (after finishing the diet period). All subjects had normal weight, body mass index (BMI) up to 25 kg/m^2 and age range between 29-51 years. Dietary restriction resulted in a statistically highly significant decrease of the mean group levels of serum TC and LDL-C levels, whereas its effect upon HDL-C and TG is slight. The decrease of LDL-C and TC did not achieve the normal values. HRV parameters: VE, HS, TP and CI are also influenced favourably but not statistically significantly in spite of the relatively long period of dietary intake (Table 3).

DISCUSSION

The accumulated (chronic) stress, assessed by HRV analysis is accepted as one of the leading factors in multifactorial genesis of coronary heart disease because of its role in development of hyperlipidemias (17, 21). On the other side the relationship between the measured level of chronic stress

Table 3. Mean values, standard errors and level of significance (P) of the HRV parameters and serum lipids, before and after administration of the diet

Parameters	Before diet		After diet		p-value
	\bar{X}_1	$S\bar{x}_1$	\bar{X}_2	$S\bar{x}_2$	
1. TC	7.33	0.44	6.17	0.23	< 0.01
2. HDL-C	1.84	0.07	1.08	0.06	< 0.05
3. LDL-C	5.18	0.44	3.77	0.19	< 0.007
4. TG	2.92	0.20	1.70	0.21	< 0.05
5. VE	1.92	0.32	1.07	0.16	ns
6. HS	0.94	0.22	1.18	0.16	ns
7. TP	5.82	0.62	7.76	0.58	ns
8. CI	-30.71	13.24	-32.71	10.53	ns
9. FA	49.43	2.94	40.68	3.26	< 0.05

(assessed by a battery of psychophysiological, clinical and paraclinical tests) and the measured level of vagal-sympathetic ratio (assessed by HRV indices) is a scientifically proved phenomenon. It was established in a long-term investigation program including several thousands of investigated persons (4, 22). As a rule stress provokes a tonic sympathetic (ergotropic) drift in the activity of the autonomic nervous system, expressed at the level of HRV by a decrease of the amount of variability of R-R intervals and augmentation of the spectral power connected with long spectral waves. The time and frequency domain-based HRV measures we used reflected those changes and proved to be a reliable body marker in this respect. The significant correlations between serum lipids and HRV parameters which were found in the experimental group (on one side) and the distress indicating values of HRV measurements in the same group (as compared with controls) (on the other side) proved that cardiovascular risk related to serum lipids is accompanied by an increased level of stress. This means that probably both factors can contribute synergically to the development of cardiovascular pathology. It would be probably possible also to use unfavourably changed HRV parameters not only for assessment of the level of stress but also for prediction of cardiovascular health risk.

As the effect of a 3-month diet is not quite favourable for other HRV-derived parameters it is possible to assume that either the diet was not administered for a sufficiently long period or it was not adequate as regards stress diminution.

It may be assumed that the effect of dietary regimes upon hypercholesterolaemia is not mediated directly through tonic changes in vagal-sympathetic balance.

Chronic sympathetic tonus accompanying hypercholesterolaemia seems to play a major role and to have a basic multifactorial origin, resulting in its resistance to dietary restrictions.

REFERENCES

1. Assmann, G.: Lipid Metabolism Disorders and Coronary Heart Disease, MMV Medizin Verlag, Munich, 1993, 282.
2. Bays, H., Dujovne, R., Lansing, A.: Drug treatment of Dyslipidemias: Practical Guidelines for the primary Care, Physician. Heart Disease and Stroke 1, 1992, 357-365.
3. Boman, B.: Stress and Heart Disease. In: Handbook of Life, Stress, Cognition and Health, S. Fisher, J. Reason (Eds.), John Willey and Sons, New York, 1988, 301-312.
4. Danev, S.: Informativeness of heart rhythm in occupational-physiology aspect. D.Sc. Thesis, Sofia, 1989.

5. Danev, S., Nikolova, R., Kerekovska, M.: Correlation between chronic distress and serum lipids. *Acta med. Bulg.* (in press).
6. Farquhar, J., Fortmann, S., Flora, J., Taylor, B., Haskell, W.: Effects of community wide education on cardiovascular disease risk factors. *J. Amer. med. Assoc.* 264, 1990, 3, 359-365.
7. Frank, E., Winkleby, M., Fortmann, S., Farquhar, J.: Cardiovascular disease risk factors: Improvement in knowledge and behavior in the 1980s. *Amer. J. publ. Hlth.* 83, 1993, 4, 590-593.
8. Frick, M., Haapa, E., et al.: Helsinki Heart Study: primary prevention trial with demfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. *New Engl. J. Med.* 317, 1987, 1237-1245.
9. Friedewald, W., Levy, R., Fredrickson, D.: Estimation of the contraction of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin. Chem.* 18, 1972, 499.
10. Hirsch, J., Mackintosh, R., Leibel, R.: Nutritionally-induced changes in parasympathetic function. *Brain Res. Bull.* 27, 1991, 541-542.
11. Kamen, P., Tonkin, A.: Application of the Poincare plot to heart rate variability: a new measure of functional status in heart failure. *Aust. N. Z. J. Med.* 1995, 25, 18-26.
12. Kannel, W., Castell, W., Cordon, T., McNamara, P.: Serum cholesterol, lipoproteins and the risk of coronary heart disease. The Framingham Study. *Ann. intern. Med.* 74, 1971, 1-12.
13. Keys, A.: Coronary heart disease in seven countries. *Circulation* 41 Suppl. 1, 1970, I-186-I-198.
14. Kleiger, R., Stein, P., Bosner, M., Rottman, J.: Time domain measurements of heart rate variability. *Ambul. Electrocard.* 3, 1992, 487-798.
15. Koskinen, P., Kupari, M., Virolainen, J. et al.: Heart rate and blood pressure variability and baroreflex sensitivity in hypercholesterolaemia. *Clin. Physiol.* 15, 1995, 483-489.
16. Malik, M.: Heart rate variability: Standards of measurement, physiological interpretation and clinical use. *Circulation* 93, 1996, 1043-1065.
17. Matthews, K., Weiss, S., Detra, T., Dembroski, T., Falkner, B., Manuck, S., Williams, R.: *Handbook of Stress, Reactivity and Cardiovascular Disease*, John Wiley and Sons, New York, 1986, 1563.
18. Moser, M., Lehofer, M., Sedminek, A., et al.: Heart rate variability as a prognostic tool in cardiology. *Circulation* 90, 1994, 1078-1082.
19. Mulder, L., Mulder, G.: Cardiovascular reactivity and mental workload. In: *The Beat-by-Beat Investigation of Cardiovascular Function*, O. Rompelman, R. Kitney (Eds.), Oxford University Press, Oxford, 1987, 216-253.
20. National Research Council: National Academy of Sciences. *Diet and Health: implications for reducing chronic disease risk*. National Academy Press, Washington DC, 1989.
21. Nikolov, N., Sudakov, K.: *Emotional Stress*. *Medizina Fiscultura*, Sofia, 1985, 190. (In Bulgarian.)
22. Nikolova, R.: *Approbation of the method for analysis of the heart rate variability under models of neuro-sensorial professional strain and its methodological improvement*. PhD Thesis, Sofia, 1993.
23. Porges, S., Byrne, E.: Research method for measurement of heart rate and respiration. *Biol. Psychol.* 34, 1992, 93-130.
24. Reinhardt, L., Makijarvi, M., Fetsch, T., Martinez-Rubio, A., Bocker, D., Block, M., Borggreffe, M., Breithardt, G.: Reduced beat-to-beat changes of heart rate: An important risk factor after acute myocardial infarction. *Cardiology*, 1996, 87, 104-111.
25. Stein, P., Bosner, M., Kleiger, R., Conger, B.: Heart rate variability: A measure of cardiac autonomic tone. *Amer. Heart J.* 127, 1994, 1376-1386.
26. Stein, K., Lippman, N., Cerman, B.: Heart rate variability and cardiovascular risk assessment. In: Laragh, J., Brenner, B. (Eds.) *Hypertension: Pathophysiology, Diagnosis and Management*. Raven Press Ltd., New York, 1995, 889-903.
27. Study Group, European Atherosclerosis Society. The recognition and management of hyperlipidaemia in adults: A policy statement of the European Atherosclerosis Society. *Europ. Heart J.* 9, 1998, 571-600.
28. Study group, EAS, Prevention of Coronary Heart Disease. *Scientific Background and New Clinical Guidelines*. *Nutr. Metab. cardiovasc. Dis.* 2, 1992, 113-156.
29. Tchasov, E., Klimova, A.: *Dyslipoproteidemias and Coronary Heart Disease*, *Medizina*, Moskva, 1980, 312. (In Russian.)
30. Tsuji, H., Larson, M., Venditti, F., Manders, E., Evans, J., Feldman, C., Levy, D.: Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* 94, 1996, 2850-2855.
31. Ueshima, H.: Changes in dietary habits, cardiovascular risk factors and mortality in Japan. *Acta cardiol.* 44, 1989, 457-477.

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