

# Allostatic Stress Load - Modulator of the Functional Association between Autonomic Cardiovascular Control and Serum Lipids in Normal Weight and Overweight

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## Abstract

The cumulative effect of allostatic stress load at work is one of the risk factors in the etiopathogenesis of Cardiovascular Diseases (CVD) and metabolic syndrome in individuals with overweight. The aim of our study is to investigate whether allostatic stress load might induce functional association between autonomic cardiovascular control and serum lipids in physicians with normal weight and overweight. The autonomic cardiovascular control, assessed with heart rate variability (HRV), and metabolic function, assessed with serum lipids profile, were examined in 33 physicians with normal weight and 31 physicians with overweight. The magnitude of correlation and regression dependencies in overweight is more pronounced between following parameters: Total Cholesterol (TC) and parasympathetic activity assessed with Spectral Power of RR intervals in Respiratory Sinus Arrhythmia band (PRSA) and baroreceptor modulation of heart rhythm assessed with sympathetically and parasympathetically mediated Spectral Power of RR intervals in the Traube-Hering-Mayer band (PTHM); and High Density Lipoprotein-Cholesterol (HDL-C) and Functional Age.

In normal weight significant correlation and regression dependency exists between TC and parasympathetic activity assessed with PRSA. Allostatic stress load causes a strong synergistic interaction between cardiovascular risk factors: overweight, autonomic cardiovascular regulation assessed by HRV and lipid profile. Significant predictor dependencies in condition of dysfunctional status of synergistically acting cardiovascular risk factors which are exacerbated by the allostatic stress load of physicians with overweight can be considered as pathophysiological mechanisms contributing to the predisposition of metabolic syndrome and risk of CVD.

**Keywords:** Heart Rate Variability; serum lipids, allostatic stress load; Cardiovascular Diseases; metabolic syndrome; physicians, normal weight; overweight; Body Mass Index

## Introduction

The chronic process of repetitive intensive stress exposure at work is associated with the resulting cost of high allostatic load inducing disturbance in physiological regulatory mechanisms, and development of pathophysiological mechanisms causing Cardiovascular Diseases (CVD), type 2 diabetes, stroke, metabolic syndrome. The fundamental risk factors for CVD are hypertension, diabetes, smoking, high blood lipid levels, low physical activity, unhealthy eating patterns, overweight or obesity, a family history for predisposition of CVD and the new dimension of stress - allostatic stress load with its functional indicator for research study - heart rate variability (HRV). The focus of our study is to determine functional dependence between certain cardiovascular risk factors as autonomic

cardiovascular control examined with HRV, serum lipids profile, and overweight modulated by allostatic stress load.

Sterling and Eyer introduce new term allostasis and postulate that the cost of homeostatic adaptation under severe stress when demands are not removed or neutralized is continuing force acting on the system causing considerable physiological effort and if the stress is not removed, the persistent effect may impair the health status [1,2]. Elliot Stellar and Bruce McEwen support the thesis of Sterling and Eyer and introduce the term allostatic load accepted to indicate the cost of long-term adaptation to chronic stressors and/or the cost of adaptation under prolonged stressful effects that could harm the health status [3]. The cost of homeostatic adaptation in the chronic process of increased

stress exposure is a high allostatic load. The cumulative effect of allostatic stress load at work is one of the risk factors in the etiopathogenesis of CVD and metabolic syndrome. Viljoen and Claasen, 2017 postulated that HRV and vagal rather than sympathetic measures of HRV should be introduced into allostatic load assessments [4].

The major risk factors for CVD include smoking, hypertension, dyslipidemia, diabetes mellitus, family predisposition to CVD, metabolic syndrome and overweight or obesity, sedentary lifestyle, stress [5]. Adverse psychological risk factors have been associated with several of the standard CVD risk factors including dyslipidemia, hypertension and overweight or obesity [6]. According to the Framingham Heart Study in individuals free of clinically apparent heart disease the HRV is an independent risk factor and contributed to the increased risk for subsequent cardiac events [7].

Hypertension remains the major preventable cause of CVD and all-caused death globally and in our continent [8]. Overweight is a risk factor in several chronic non-communicable diseases today, diseases that are the leading causes of death in much of the world, including in our country. Elevated serum Total Cholesterol and Low-Density Lipoprotein-Cholesterol (LDL-Cholesterol) are factors contributing to the development of CVD. Disorders of lipid metabolism increase the cardiovascular health hazard for CVD by facilitating the endothelial injury of the vascular wall and the proliferation of vascular smooth muscle cells [9].

The aim of our study is to investigate whether allostatic stress load might induce functional association between autonomic cardiovascular control and serum lipids in physicians with normal weight and overweight. In our study we will study whether the effect of allostatic stress load, might cause interaction between cardiovascular risk factors, namely the interaction between overweight, autonomic cardiovascular control examined with HRV, and lipid profile. The study will test the hypothesis that the allostatic stress load might modulate the functional association between pre-abnormal autonomic cardiovascular control and atherogenic biochemical lipid abnormalities in individuals with normal and overweight. The proposition inherent in our hypothesis is that the complex synergistically interaction between cardiovascular risk factors: allostatic stress load, pre-abnormal autonomic cardiovascular control, serum lipids, and overweight might induce risk of metabolic syndrome and risk of CVD.

## Materials and Methods

Two groups of subjects participated in the study: physicians with normal weight and overweight. The body mass index (BMI) is measured in kilograms per square meter and is determined by the following formula:  $BMI = W/h^2$ , where BMI is Body Mass Index; W – weight in kilograms; h - height in meters. Normal values for BMI are between 18.5 - 24.9 kg/m<sup>2</sup>. For overweight

we talk about BMI from 25.0 to 29.9 kg/m<sup>2</sup>. Above BMI > 30 kg/m<sup>2</sup> there is already obesity. In our study BMI is a discriminating variable dividing the whole group into two sub-groups: normal weight and overweight.

The first sub-group: normal weight consisted of 33 male physicians whose ages ranged from 27 to 52 years (mean age,  $X \pm SD$ , 42.17  $\pm$  10.09 yr). The second sub-group: overweight consisted of 31 male physicians, who were matched for age (mean age,  $X \pm SD$ , 42.12  $\pm$  9.12 yr) to the first sub-group. The research study including human experimentation was done in accordance with the institutional review body of Medical University Sofia and carried out with the ethical standards of the Ethics Committee of Scientific Research at the Medical University, Sofia.

## Autonomic Cardiovascular Control is Studied with Heart Rate Variability (HRV)

A computerized diagnostic system for the study of autonomic cardiovascular function was applied [10,11]. HRV data were determined from ten minutes of ECG recordings between 9 a.m. and 11 a.m. in supine position after a one-hour rest period.

Following indices were analyzed:

### Time-Domain HRV Measures

- a) X (mean RR interval) (milliseconds), resp. mean heart rate (beats per minute);
- b) Short-Term Variability (STV) (m sec) (reflecting respiratory oscillations in heart rate variations) (parasympathetically mediated).

### Frequency-Domain HRV Measures

- i. Spectral power of RR intervals in the Temperature band (0.01-0.05 Hz) (PT) (sympathetically mediated) (milliseconds<sup>2</sup>);
- ii. Spectral power of RR intervals in the Traube-Hering-Mayer band (0.06-0.14 Hz) (PTHM) (sympathetically and parasympathetically mediated) (milliseconds<sup>2</sup>);
- iii. Spectral power of RR intervals in the Respiratory Sinus Arrhythmia band (RSA) (0.15-0.50 Hz) (PRSA) (parasympathetically mediated) (milliseconds<sup>2</sup>). Spectral powers of RR intervals in the respective frequency bands were calculated using Fast Fourier Transform.

### HRV-Derived Indices

- a) Physical Stress (PS) (mathematical algorithm based on difference between measured and age-referent values derived from the time-domain HRV measures) (arb. un.);
- b) Mental Stress (MS) (mathematical algorithm based on difference between measured and age-referent values derived from the frequency-domain HRV measures) (arb. un.);

c) Functional Age (FA) (mathematical algorithm computing difference between measured and age-referent values of autonomic activity derived from the frequency-domain HRV measures) (years);

d) Health Risk (HR) (%) (mathematical algorithm derived from PS-, MS-coefficients and number of premature heart beats) (%).

### Serum Lipids

Total Cholesterol (TC) (nmol/l) - investigated by an enzymatic colorimetric method using the Roche apparatuses; Low Density Lipoprotein-Cholesterol (LDL-C) (nmol/l) investigated by Roche's homogeneous enzyme colorimetric method; High Density Lipoprotein-Cholesterol (HDL-C) (nmol/l) investigated by Roche's homogeneous enzyme colorimetric method; Triglycerides (TG) (nmol/l) investigated by an enzymatic colorimetric method using Roche apparatuses; TC/HDL-C ratio.

### Data Analysis

To determine correlations between HRV variables, and serum lipids Spearman's correlation analysis was applied. Dependencies of serum lipids on HRV variables were determined by linear regression analysis. A p value < 0.05 was considered statistically significant.

### Results

#### Autonomic Cardiovascular Control Differences in Physicians with Normal Weight and Overweight

To discriminate basic types of allostatic stress load-induced autonomic cardiovascular modes of control, the autonomic cardiovascular control is differentiated based on HR values: referent - HR ≤ 25%; pre-abnormal - HR ≥ 25% - ≤ 65%; and abnormal - HR ≥ 65%. Although the difference is not statistically significant the HR value in the first sub-group: normal weight is 49.58 %, and in the second sub-group: overweight is 64.26 % and corresponds to the pre-abnormal (dysfunctional) mode of control.

#### Correlations Between Serum Lipids and HRV Parameters in Physicians with Normal Weight and Overweight

In first sub-group: normal weight was observed following correlation of PRSA, and TC:

i. Significant correlation of TC with PRSA: (r=-0.591, p=0.04).

In second sub-group: overweight the number of correlations between HRV variables, and serum lipids increased. The correlations were:

i. Significant correlation of TC with: STV(r=-0.457, p=0.03); PTHM (r=-0.562, p=0.005); PRSA (r=-0.469, p=0.002); PS (r=0.522, p=0.01); FA (r=0.63, p=0.001); HR

(r=0.519, p=0.01);

ii. Significant correlation of HDL-C with: FA (r=0.496, p=0.01);

iii. Significant correlation of LDL-C with: STV (r=-0.444, p=0.04); PTHM (r=-0.524, p=0.01); PRSA (r=-0.441, p=0.04); PS (r=0.662, p=0.001); FA (r=0.616, p=0.003); HR (r=0.491, p=0.02) ;

iv. Significant correlation of TC/HDL-C with: PS (r=0.564, p=0.006); MS (r=0.483, p=0.02).

Significant correlations were found in both sub-groups but the correlations between cardiac and lipid parameters prevail in the second sub-group. In physicians with normal weight the parasympathetically mediated PRSA negatively correlated with TC. In second sub-group: overweight the parasympathetically mediated STV and PRSA negatively correlated with TC and LDL-C; the baroreceptor modulation of heart rhythm assessed with sympathetically and parasympathetically mediated PTHM also negatively correlated with TC and LDL-C. In the same sub-group strong correlations exist between stress indices: MS, PS, FA, HR and TC, LDL-C, HDL-C, and TC/HDL-C ratio.

#### Functional Dependencies of Serum Lipids on HRV Parameters in Physicians with Normal Weight and Overweight

**Table 1:** Regression equations of dependencies of serum lipids on HRV variables.

Normal Weight	
<b>1. Dependence of TC on PRSA</b>	
PRSA = 190.22 - 19.09*.TC (B: p=0.04)	
Overweight	
<b>1. Dependence of TC on STV, PTHM, PRSA, PS, FA, and HR</b>	
STV = 65.34 - 4.93*.TC (B: p=0.03)	
PTHM = 161.55 - 13.59**.TC (B: p=0.005)	
PRSA = 170.7 - 15.37*.TC (B: p=0.02)	
PS = - 4.43 + 1.07*.TC (B: p=0.01)	
FA = 19.07 + 5.68**. TC (B: p=0.001)	
HR = 27.27 + 6.07*.TC (B: p=0.01)	
<b>2. Dependence of HDL-C on FA</b>	
FA = 31.66 + 20.78*.HDL-C (B: p=0.01)	
<b>3. Dependence of LDL-C on STV</b>	
STV = 53.95 - 4.67*.LDL-C (B: p=0.04)	

Functional dependencies of serum lipids on HRV variables were determined by linear regression analysis. Regression equations are presented in Table 1. We found a predominance of dependencies between cardiac and lipid variables in physicians with overweight. In the first sub-group: normal weight significant regression dependence of TC on parasympathetically mediated PRSA was observed. Contrary to this finding in the second sub-group significant dependencies of TC on STV, PTHM, PRSA, PS,

FA, and HR; HDL-C on FA; and LDL-C on parasympathetically mediated STV were observed. The association between baroreceptor modulation of heart rhythm assessed with sympathetically and parasympathetically mediated PTHM and parasympathetically mediated PRSA and TC, and between FA and HDL-C were more pronounced in the second sub-group.

## Discussion

The ultimate effect of the chronic process of repetitive intensive stress exposure, which is associated with the daily and even 24-hour work of physicians is allostatic stress load inducing interaction between autonomic cardiovascular control and metabolic lipid function in both sub-groups. The allostatic stress load affected the process of complex interaction between cardiovascular risk factors such as overweight, pre-abnormal autonomic cardiovascular control, atherogenic lipid profile, and exerted multiplicative and synergistic effect of risk factors on health status rather than an additive one.

We found a negative correlation between the parasympathetic activity assessed by PRSA and TC in physicians with normal weight, but in physicians with overweight correlations increased as the parasympathetic activity assessed by PRSA and STV correlated negatively with TC and LDL-C. In physicians with overweight the baroreceptor modulation of the heart rhythm assessed with sympathetically and parasympathetically mediated PTHM is negatively correlated with TC and LDL-C. However, in the same sub-group, positive correlations are found between MS, PS, FA, HR (markers of sympathetic activation) and most indicators evaluating the lipid profile: TC, LDL-C, HDL-C, and TC/HDL-C ratio.

Negative correlations between PTHM reflecting sympathetic and parasympathetic tone, and PRSA which represents autonomic parasympathetic tone and BMI are found from Laederach Hofmann et al. [12], and Peterson et al. [13]. Contrary to these findings Rossi et al., 1989 could not find any differences in sympathetic function [14]. Badea [15] and Zahorska Markiewicz et al. [16] found that TC and LDL-C were associated with rMSSD and PRSA as markers of parasympathetic function and with PT as marker of sympathetic activity which is in accord to our study. These results indicate that allostatic stress load causes a strong synergistic interaction between cardiovascular risk factors. The synergistic interaction between risk factors is enhanced by the established predictive dependencies of: TC on sympathetic, parasympathetic activities and baroreceptor modulation of heart rhythm (STV, PTHM, PRSA, PS, FA, and HR); LDL-C on parasympathetic activity mediating STV; and HDL-C on FA, which form pathophysiological mechanisms affecting cardiovascular and metabolic status.

Our finding of independent inverse relation between the parasympathetic activity assessed with STV and LDL-C is consistent with the result of Kupari et al. [17] who observed dependence between the rMSSD and LDL-C [17]. The importance

of lowered parasympathetic activity as a factor exerting deleterious effect on metabolism, psychosocial functioning and survival in obesity is highlighted in a study of metabolic syndrome by Bjorntorp [18]. Our result of initiation of pathophysiological mechanisms inducing metabolic syndrome and risk of CVD in physicians is supported by the result of Brotman et al. [19] who indicates that stress triggers pathophysiological mechanisms that include altered metabolic and cardiac autonomic control [19].

## Conclusion

The results of our study revealed that allostatic stress load induced significant functional association between autonomic cardiovascular control and serum lipids in physicians with normal weight and overweight. Significant predictor dependencies in condition of dysfunctional status of synergistically acting cardiovascular risk factors such as overweight, pre-abnormal autonomic cardiovascular control, and atherogenic lipid profile which are exacerbated by the allostatic stress load can be considered as pathophysiological mechanisms disturbing tissue metabolism and contributing to the predisposition of metabolic syndrome and risk of CVD. The observed dependencies in their functional role of pathophysiological mechanisms can be considered as precursors of the metabolic syndrome and the risk of CVD.

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