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## SURVIVAL OF PATIENTS WITH CHRONIC ISCHEMIC HEART DISEASE DEPENDING ON THE TYPE OF ADAPTATIONAL REACTION

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### Abstract

The aim of investigations was to study survival of patients with chronic ischemic heart disease (IHD) depending of the type of adaptational reaction. It was studied correlations between the type of adaptational reactions and the clinical course of chronic IHD in 121 male patients in long-term prospective observation. The diagnosis of IHD was based on clinical examinations, laboratory investigations, electrocardiography, echocardiography, exercise testing, coronary angiography. It was revealed, that distress-reactions (stress, over-activation and defective adaptation) are significant predictors of an unfavorable chronic IHD prognosis. They were associated with acute cardiovascular events onset, functional class III of chronic heart failure, prothrombotic disorders of coagulation haemostasis (high levels of fibrinogen, fibrin-monomer and D-dimer), and dyslipidemia (lower HDL-cholesterol values). Decreasing of lymphocyte/neutrophil ratio (index of adaptation) is an informative parameter of distress-reactions and a significant predictor of an unfavorable chronic IHD course.

**Key words:** adaptational reactions, stress, ischemic heart disease prognosis, fibrin-monomers, lymphocyte/neutrophil ratio.

**Introduction.** Ischemic heart disease (IHD) remains the one of the most important medical and social problems and the leading cause of mortality in most industrialized countries. Despite the high rate of success in the treatment of IHD, patients suffering from

stable angina are still in danger of nonfatal complications and sudden death, that require finding informative prognostic criteria course of coronary artery disease. Considering the major cardiovascular risk factors, doctors often do not pay attention on stress factors, which contribute to the occurrence of cardiovascular diseases. The channel cardiovascular stress realignment, which occurs under conditions of stress reactions and other adverse reactions types of adaptation is caused by changes in key regulatory adaptation - the nervous, endocrine, immune. This creates prerequisites for the emerge and progress of major cardiovascular disease continuum - coronary heart disease and its complications of congestive heart failure [1-6]. Diagnosis of the type of adaptive responses allows to predict the course diseases and justify the correct treatment [6]. However, the predictive value of total non-specific adaptation reactions in patients with coronary artery disease remain poorly studied.

**The aim** of our investigations was to study survival of patients with chronic ischemic heart disease (IHD) depending of the type of adaptational reaction.

**Materials and methods.** This study involved 121 male patients aged 36-78 years (median 59 years) diagnosed with chronic IHD: stable angina of functional class I-III (n=49), prior myocardial infarction (n=52), after coronary bypass surgery and stenting (n=20). The course of IHD was complicated by chronic heart failure New York Heart Association (NYHA) functional class (FC) I-III. The diagnosis of IHD was based on clinical examinations, laboratory investigations, electrocardiography, echocardiography, exercise testing, coronary angiography.

The level of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG) were determined spectrophotometrically by using enzymatic reagents firm "Pointe Scientific" (USA), low-density lipoprotein-cholesterol (LDL-C) was calculated by Friedewald formula (1972). We examined parameters of platelet hemostasis: platelet count in peripheral blood and their aggregation with ADP (A.S. Shytykova, 1984). The fibrinogen

concentration was determined by the gravimetric method of R.A. Rutberg (1961), soluble fibrin-monomer (FM) – ortofenantrolin test (Technology Standard, Russia) [7], D-dimer – by the immunoferment analysis (TECHNOZYM D-dimer ELISA, Austrian) [8]. Also we determined the ethanol gelation test and prothrombin index [7]. Glomerular filtration was calculated by using formula:  $186 \times \text{serum creatinine in mg/dL}^{-1,154} \times \text{age}^{-0,203}$  [9]. The type of adaptational reaction was determined by an index of adaptation (lymphocytes to segmented neutrophils counts ratio) [6,10]. Stress-reaction was defined due to index of adaptation  $<0,30$ ; orientation  $0,31-0,50$ ; quiet activation  $0,51-0,70$ ; raised activation  $0,71-0,90$ ; over-activation  $>0,90$ . Defective adaptation reaction was detected in leukopenia cases. Reactions of stress, over-activation and defective adaptation were considered as distress-reactions, quiet and raised activation - as eustress-reactions [6].

Statistical analysis was done using Statistica for Windows 5.0 (Statsoft, USA). Data are presented as the median [lower-upper quartiles], comparisons between groups were made using the Mann-Whitney U-test. Categorical data were assessed using the Fisher exact test, the correlation between variables - by Kendall's correlation test, survival curves during 36 months - by the Kaplan-Meier method with significant difference between the groups - by Cox's F-test and Hehan-Wilcoxon test.

**Results.** Among IHD patients stress-reaction was registered in 21 (17%) patients, orientation – in 38 (32%), quiet and raised activation – in 50 (41%), over-activation – in 12 (10%) patients. Reactions of defective adaptation was not recorded at all. General non-specific adaptational reactions differed according to clinical characteristics. Chronic heart failure of FC III was revealed more frequently in patients with stress-reaction (43%), whereas in patients with orientation (24%), quiet and raised activation (8%), over-activation (25%) less often (the difference is statistically significant between stress-reaction and quiet and

raised activation,  $p=0,007$ ). This finding is consistent with our previous studies which have demonstrated increasing frequency heart failure FC III in patients with stress-reactions [6].

After initial examination, long-term observation for the patients was provided: during 12 months on 81 (67%), 24 months – on 24 (20%), and 36 months – on 16 (13%) individuals. During this time in 20 (17%) of patients acute cardiovascular events were registered (acute coronary syndrome in 13, stroke in 5, peripheral thrombosis in 2), which were taken as the end-point of observation. These acute cardiovascular events occurred during first 6 months in 15 (75%), from 6 to 12 months in 1 (5%), from 12 to 36 months in 4 (20%) patients. It was estimated, that the patients with and without acute cardiovascular events did not differ significantly in age, presence of any arrhythmia, previous Q-infarction, diabetes mellitus, obesity, severity of heart failure FC I-III, and their management. But in patients with acute cardiovascular events stress-reaction was observed more frequently (50%), whereas in patients without acute events – quiet and raised activation (47%) (**table 1**).

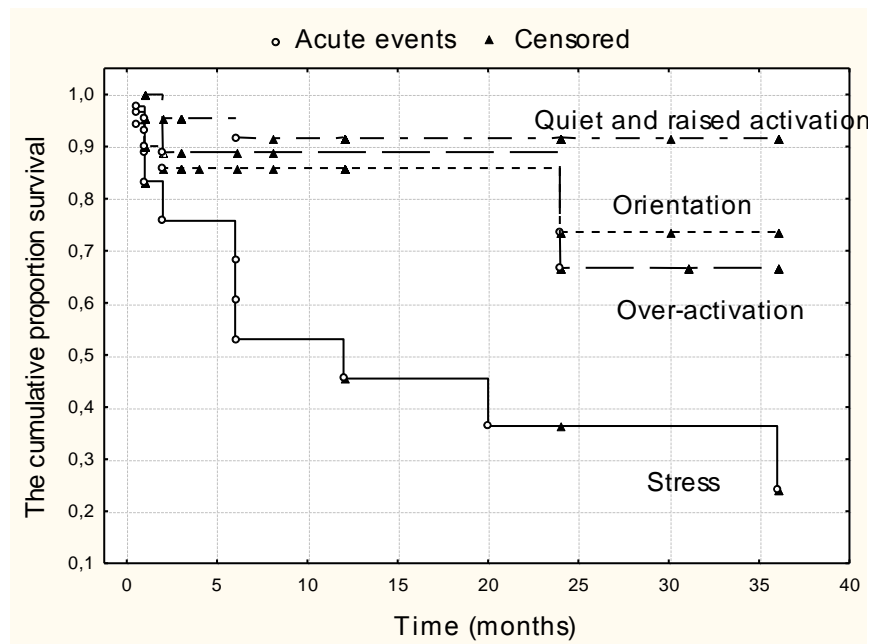
**Table 1. The frequency of adaptation reactions in patients with and without acute cardiovascular events**

Type of adaptational reactions	Patients with acute cardiovascular events, % (n)	Patients without acute cardiovascular events, % (n)
Stress	50 (10) <sup>1</sup>	11 (11) <sup>1</sup>
Orientation	25 (5)	33 (33)
Quiet and raised activation	15 (3) <sup>2</sup>	47 (47) <sup>2</sup>
Over-activation	10 (2)	10 (10)
<b>Total</b>	100 (20)	100 (101)

*Notices: 1 -  $p=0,0002$ ; 2 -  $p=0,01$ .*

Retrospective analysis of prognostic value of all clinical and laboratory parameters showed that stress-reaction was the significant predictor of future acute cardiovascular events in patients with chronic IHD. Three-year survival was significantly greater in patients with eustress-reactions. The cumulative survival proportion in patients with stress-reaction was

35.5%, whereas in patients with orientation – 68.4%, over-activation – 63.0%, quiet and raised activation – 90.7%. There were significant differences between stress-reaction and orientation (Cox's F-test,  $p=0,01$ ; Hehan-Wilcoxon test,  $p=0,04$ ), quiet and raised activation (Cox's F-test,  $p=0,003$ ; Hehan-Wilcoxon test,  $p=0,001$ ) (**figure 1**).



**Figure 1. Survival of patients with chronic IHD depending on the type of adaptational reactions**

We revealed also that heart failure of III FC, atrial fibrillation, ejection fraction  $<45\%$ , left ventricle diastolic diameter  $\geq 6$  cm, levels of fibrinogen  $>4$  g/L, fibrin monomer  $\geq 4$  mg/dL, D-dimer  $\geq 120$  ng/mL, total cholesterol  $<5,2$  mmol/L, high density lipoprotein cholesterol  $<1,0$  mmol/L, ESR  $>12$  mm/h, glomerular filtration  $\leq 60$  ml/min were significant predictors of worse survival during first three years of observation (**table 2**).

**Table 2. Predictors of survival patients with chronic IHD**

Predictors	Cumulative proportion survival	Predictors	Cumulative proportion survival	Cox's F - test	Hehan-Wilcoxon test
Heart failure III FC	63,1 %	Heart failure I-II FC	78,5 %	p=0,05	p=0,06
Atrial fibrillation	20 %	No atrial fibrillation	72,2 %	p=0,003	p=0,004
Ejection fraction <45%	46,3 %	Ejection fraction $\geq$ 45%	73,6 %	p=0,05	p=0,06
Left ventricle diastolic diameter $\geq$ 6 sm	55,8 %	Left ventricle diastolic diameter <6,0 sm	86,7 %	p=0,001	p=0,02
Fibrinogen >4 g/L	61,5 %	Fibrinogen $\leq$ 4 g/L	80,3 %	p=0,02	p=0,056
Fibrin monomer $\geq$ 4 mg/dL	55,6 %	Fibrin monomer <4 mg/dL	100 %	-	p=0,0001
D-dimer $\geq$ 120 ng/mL	23,3 %	D- dimer <120 ng/mL	58,8 %	p=0,01	p=0,05
Total cholesterol <5,2 mmol/L	53,7 %	Total cholesterol $\geq$ 6,2 mmol/L	96,7 %	p=0,09	p=0,007
HDL-C <1,0 mmol/L	51,4 %	HDL-C $\geq$ 1,0 mmol/L	86,8 %	p=0,037	p=0,05
Glomerular filtration $\leq$ 60ml/min	38,2 %	Glomerular filtration >60 ml/min	82,1 %	p<0,0001	p=0,0001
ESR >12 mm/h	53,5 %	ESR $\leq$ 12 mm/h	78,7 %	p=0,02	p=0,06

Atrial fibrillation and systolic dysfunction (ejection fraction <45%) were also potent predictors of worse survival during first year of observation.

Index of adaptation correlated with functional class of heart failure ( $\tau=-0,163$ ; p=0,008); left ventricle diastolic diameter ( $\tau=-0,153$ ; p=0,01); fibrin monomer level ( $\tau=-0,301$ ; p<0,0001); fibrinogen level ( $\tau=-0,155$ ; p<0,05); D-dimer level ( $\tau=-0,201$ ; p<0,05).

According to the literature data, stress is associated with hypercoagulation due to an activation of platelets, increasing concentration of von Willebrand factor, fibrinogen, VII factor of coagulation and inhibition of fibrinolysis system [1-4]. In our study, the stress-reaction was also associated with prothrombotic disorders of coagulation. We found higher concentration of fibrin monomer (median 10.5 mg/dL), fibrinogen (median 4.2 g/L), D-dimer

(median 212.0 ng/mL) in patients with stress-response (significant difference compared with other adaptational reactions,  $p < 0,05$ ) (table 3).

**Table 3. Parameters of hemostasis in patients with IHD and different adaptational reactions**

Parameters of hemostasis	Type of adaptational reactions			
	Stress	Orientation	Quiet and raised activation	Over-activation
Platelet count, $\times 10^9/L$	237,0 [169,5-285,0]	239,5 [197,5-270,5]	229,0 [212,0-278,0]	214,2 [200,0-230,0]
Platelet aggregation, sec	16,4 [11,0-18,0]	12,9 [10,0-17,2]	12,4 [11,0-16,2]	15,4 [12,6-18,1]
Platelet aggregation, sec (aspirin)	18,0 [11,2-22,5]	16,0 [10,4-19,6]	16,0 [12,0-20,0]	13,6 [13,4-16,0]
Fibrinogen, g/L	4,2 [3,5-5,0] *	4,0 [3,5-4,5]	3,5 [3,0-4,2] *	3,9 [3,5-4,2]
Fibrin monomer, mg/dL	10,5 [6,0-15,0] <sup>123</sup>	4,0 [3,4-5,0] <sup>1</sup>	3,4 [3,4-4,0] <sup>2</sup>	4,0 [3,4-5,5] <sup>3</sup>
D-dimer, ng/mL	212,0 [70,0-250,0] *	52,0 [30,0-85,0]	30,0 [20,0-77,5] *	90,9 [45,0-237,5]
Ethanol gelation test, standard units	0 [0-1]	0,5 [0-1]	0,5 [0-1]	0,5 [0-1]
Prothrombin index, %	89,0 [83,0-94,0]	99,0 [94,5-100,5]	97,0 [91,5-100,0]	95,0 [76,0-99,0]

Notices: \* -  $p < 0,05$ ; <sup>1 2 3</sup> -  $p < 0,0001$ .

Increased levels of fibrin monomer ( $\geq 4$  mg/dL) occurred in 20 (95%) patients with stress-reaction, in 23 (60%) with orientation, in 17 (34%) with quiet and raised activation and in 5 (42%) with over-activation (significant difference between stress and other types of adaptational reactions,  $p < 0,05$ ). Our results did not support an association between the stress response and parameters of thrombocytic hemostasis (platelet count and their aggregation).

According to the literature data, type of adaptational reactions is associated with lipid metabolism parameters, which are important prognostic factors for coronary artery disease course [11]. But in our study, correlations of index of adaptation and total cholesterol ( $\tau = 0,11$ ,  $p = 0,08$ ) or HDL-cholesterol ( $\tau = 0,13$ ,  $p = 0,07$ ) levels did not reach statistical significance. However, in patients with stress response HDL-cholesterol value was significantly lower than

in patients with quiet and raised activation (0.9 [0.8-1.1] mmol/L and 1.2 [1.1-1.5] mmol/L,  $p=0.006$ ).

**Conclusions.** Distress-reactions were observed more often in patients with IHD than eustress-reactions (68% and 8%,  $p<0.05$ ). Stress-reaction is a significant predictor of an unfavorable IHD prognosis. Unfavorable IHD course was associated with functional class III chronic heart failure, dilatation of the left ventricle, prothrombotic disorders of coagulation haemostasis (high levels of fibrinogen, fibrin monomer and D-dimer), and dyslipidemia (lower HDL-cholesterol values). In 50% patients with acute cardiovascular events stress-reaction was observed. Index of adaptation (lymphocytes to segmented neutrophils counts ratio) can be one of the criteria for IHD prognosis.

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