On The State of the Sympathetic-Adrenal System and Cytokine Status in Patients with Ischemic Heart Disease by Familial Hypercholesterolemia

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ABSTRACT

The article presents the features of disorders of the sympathetic-adrenal system and cytokine status in patients with ischemic heart disease and familial hypercholesterolemia. The study included 144 men and women aged 18 to 65 years, with an average age of 43.8±7.2 years and 15 practically healthy individuals aged 20 to 50 years, with an average age of 41.4±3.5 years. Clinical, instrumental and special research methods were performed. It was found that familial hypercholesterolemia has marked changes in the sympathoadrenal system and cytokine status, which are more pronounced in patients with AHS with clinical signs of CHD.

Keywords: Family hypercholesterolemia, coronary heart disease, sympathetic adrenalsystem, catecholamines, cytokines.

In recent years, there has been a re-evaluation of the key provisions of the pathogenesis of atherosclerosis and coronary heart disease. It has been established that inflammation is the most important sign of the development of atherosclerosis, which can determine its progression and lead to vascular dysfunction and plaque rupture, followed by thrombotic occlusion and the development of cardiovascular complications (Alekperov E. Z. et al., 2014; CenturionO.A., 2016). It has been established that the effect of hyperproduction of proinflammatory cytokines on the progression of CHD is realized by direct damaging effects exerted primarily by tumor necrosis factor-a(TNF-a), interleukins (IL) -1, -6 on cardiomyocytes and peripheral tissues of the human body, modulation of the activity of neurohumoral systems (in particular, CAC and RAAS), production of nitric oxide (NO) and other metabolic factors. Recent studies suggest that understanding the pathogenesis of CHD requires further study of circulatory regulatory systems, in particular the sympathetic-adrenal system (CAS). Data on the effect of catecholamines (CA) on the development of cellular or humoral immune responses are scarce. According to them, it can be assumed that as a result of the development of the stress response, the processes of immuno-inflammatory reactions are suppressed.

Research objective: To study the state of SAS and levels of pro-and anti-inflammatory cytokines in CHD patients with familial hypercholesterolemia (FHCH).

Materials And Methods

The study included 144 people with AHS: 96 men, 48 women aged 18 to 65 years, with an average age of 43.8±7.2 years, and 15 practically healthy individuals aged 20 to 50 years, with an average age of 41.4±3.5 years. The study included patients over 18 years of age with definite and probable CHD, according to the criteria of the Dutch Lipid Clinic Network (DLCN), depending on the manifestations of clinical signs of CHD, the subjects were randomized into 3 groups: I-control, healthy, n=15; II-CHD without signs of CHD, n=56

(38.9,9%III-AHS with signs of CHD, n=98 (61.1%). Total cholesterol, high – density lipoproteins (HDL), and triglycerides (TG) were determined using biochemical rapid analyzers "ReflotronPlus" ("Rowithhe", Germany). The content of LDL and VLDL was calculated according to the formula of A. N. Klimov. Daily urinary excretion of free and conjugated forms of catecholamines (CA) was studied by fluorimetric method.

Determination of LPO products in blood serum was performed by the method of B. V. Gavrilov. Determination of MAO in blood serum was carried out by the method of A. I. Balakleevsky. Cytokine status was determined by the level of interleukins IL-6, IL-10, and FNL-α in blood serum by solid-phase enzyme immunoassay. Non-specific inflammation was determined by the level of highly sensitiveC-reactive protein (hf-CRP) by immunoturbodimetric method using kits from the company "Vector-Best "(Novosibirsk, Russia). CStatistical processing of the obtained results was carried out using Student's criteria.

Results And Discussions

Comparative characteristics of the blood lipid spectrum indicators of the studied groups are shown in Table 1.

Table 1

Some clinical and biochemical parameters of lipids and lipid peroxidation products in the blood serum of patients with CHD and healthy subjects (P<0.001).

Indicators	**Healthy (n=15)**	**CHD without C (n=56)**	**CHD with CHD (n=98)**
Tendon xanthomas, abs (%)	-	44 (78,6)	89 (91)
OXCTC, mmol/L	4,5±0,3	7,5±1,2*	8,23±1,3^
TG, mmol/L	1,3±0,1	1,6±0,1*	1,8±0,1^
LDL CHOLESTEROL, mmol/L	3,1±0,3	6,3±0,4*	6,9±0,4^
HDL CHOLESTEROL, mmol/L	1,3±0,1	1,0±0,1*	1,1±0,1^
VLDL CHOLESTEROL, mmol/L	0,28±0,02	0,34±0,02*	0,36±0,02^
IA, u	3.1±0,1	6.4±0,2*	6.7±0,2^
MDA, nmol / l	3,6±0,5	6,2±0,8*	7,8±0,7^

Note: IA - atherogenicity index; MDA – malondialdehyde;*, ^ - differences in relation to the control group are significant (P<0.001).

When studying the daily excretion of CA and DOPA, the following changes were observed (Table 2). In IIGroup II, there was a statistically significant (p<0.001) increase in the daily excretion of epinephrine (A) free by 24.4%, conjugated by 28.9% and total by 26.5% in relation to the control group. The excretion of free norepinephrine (HA) increased by 12.1%, conjugated - by 16.8% and total-by 14.4% in relation to the control group (p<0.001). Dopamine (DA) free, conjugated, total increased by 8.5%, 10,%, and 9.3%, respectively, in relation to the control group (p<0.05). DOPA increased by 4.5% in relation to the control group (p<0.001). In IIIgroup III, there was a decrease in the daily excretion of catecholamines, in particular; free by 31.1%, conjugated by 23.7%, total by 27.7% in relation to the control group (p<0.001). Free, conjugated, and total weight was reduced by 31.3%, 25.3%, and 29.3%, respectively, compared with healthy subjects (p<0.001). There is a decrease in DA excretion: free - by 51.1%, conjugated - by 46.6%, total-by 48.8% in relation to the control (p<0.001). DOPA was reduced by 22.0% compared to group I (p<0.001).

The study of MAO activity in patients with AHS revealed a significant decrease in the activity of the enzyme in all the examined groups in relation to the control group (Table 2). In the control group, MAO activity was 0.07

±-0.001 u/ ex. In IIgroup II, MAO activity was 0.05±-0.003 u/ ex, which is 28.6% lower than the control (p<0.001). In IIIgroup III, there was a significant decrease in the activity of the enzyme by 42.9% compared to the control group and amounted to 0.04±-0.004 u/ ex. (p<0.001).

Indicators of LPO in all study groups significantly differed from those in the control group. In the control group, the level of malondialdehyde(MDA), a secondary product of LPO, ranged from 2.1 – 4.4 nmol/ml, with an average of 3.6±0.5 nmol/ml. In group II, there was a statistically significant increase in the level of MDA by 72.2% compared to the control group (p<0.001). In IIIGroup III, there was an increase in the level of MDA by 116.6 % in relation to the control indicators (p<0.001) (Table 1).

Table 2

Daily excretion of CA and MAO activity in healthy subjects and patients with CHD, P<0.001

group	**A, mcg/day**	**NA, mcg / day**	**DA, mcg / day**	**DOPA, mcg / day**	**MAO, u/ ex**
I-Control				46.4±0.6	0.07±0.001
free	4.5±0.1	9.9±0.1	140.4±5.2		
conjugated	3.8±0.1	8.7±0.1	152.8±5.5		
total	8.3±0.2	18.8±0.2	292.2±9.4		
II- SGHS without CHD				48.5±0.8	0.05±0.003
free	5.6±0.1	11.1±0.1	152.4±6.3		
conjugated	4.9±0.1	10.4±0.1	167.0±5.2		
total	10.5±0.2	21.5±0.4	319.4±10.0		
III-AHS with CHD				36.2±0.6	0.038±0.003
free	3.1±0.1	6.8±0.1	68.6±3.2		
conjugated	2.9±0.1	6.5±0.1	81.1±4.1		
total	6.0±0.2	13.3±0.2	149.7±7.4		

In our study, indicators of non – specific inflammation-cytokines: IL-6, IL-10, FNL-α, and hf-CRP-were evaluated in patients with ACS.

Table 3

Indicators of cytokines IL-6 and IL-10 in blood serum in patients with CHD without CHD

Indicators	of the Group of patients		
	with CHD without CHD (n=56)	Control (n=15)	P
IL-6 (pg / ml)	15.3±2.1,1	8.5±0.9	<0.001
IL-10 (pg / ml)	8,4±0,4	8,2±0,7	>0,05

Table 4

Indicators of cytokines IL-6 and IL-10 in blood serum in patients with CHD

Indicators	of the Group		
	of CHD patientswith CHD (n=98)	Control (n=15)	P
IL-6 (pg / ml)	24.5±0.9	8.5±0.9	<0.001
IL-10 (pg / ml)	8,1±0,7	8,2±0,7	>0,05

БTNF-α and hf-CRP were studied in patients with AHS without and with CHD. A comparative assessmentof TNF-alpha and hf-CRP values in blood serum in healthy and AHS patients without clinical signs of CHD showed that in patients with AHS, the levels of TNF-alpha and CRP were 13.4±2.2 and 2.7±0.1, which is 1.76 times (p<0.001) and 2.5 times (p<0.001), respectively.0.001) is higher than the control indicators (Table 5). Such trends are more pronounced in the group of patients with CHD with clinical signs of CHD (Table 5). Thus, the level of FNO-α in patients averaged 18.5±1.8, which is 2.4 times higher (p<0.001) than the control indicators and the average value of hf-CRP was 3.8±0.1 mg / ml, which is 3.45 times higher (p<0.001) than the control parameters.

Table 5

FN-O-α and hf-CRP values in blood serum in patients with AHS

Indicators	of the Group of examined individuals			
	CHD without CHD (n=56)	CHD with CHD (n=98)	Control (n=15)	P
FNO-α (pg / ml)	13,4±2,2	18,5±1,8	7,6±0,7	<0,001
hf-CRP (mg / ml)	2,7±0,1	3,8±0,1	1,1±0,1	<0,001

Thus, the problem of the functional state of SAS in patients with CHD, its relationship with the features of the course of the disease, the formation of complications is the subject of discussion. One of the central places in the complex interaction of various regulatory systems belongs to SAS, which is associated with the widest range of its effects [6]. Activation of SAS, through direct trophic effects, is accompanied by a number of structural changes, primarily in the vascular wall and myocardium. Structural changes in blood vessels are directly involved in the formation of myocardial ischemia, stroke, and damage to other target organs [11].

An increase in the activity of SAS in familial hypercholesterolemia can be regarded as compensatory, ensuring the mobilization of the body's defenses, increasing the energy supply to the myocardium. A further increase in the intensity of CAC activity is aimed at mobilizing the internal reserves of the body. However, at one of the stages of this process, the catabolic orientation of the effects of SAS begins to manifest, and the further increase in the activity of which becomes one of the main elements of the formation of CHD and its complications.

The results of the conducted studies showed that in case of AHS, there is a moderate activation of CAC associated with an increase in the excretion of catecholamines: A, HA, DOPA by 1.27; 1.14; 1.05 times, respectively ($p<0.001$), DA by 1.09 times ($p<0.05$) in relation to healthy people. These data coincide with the data of L. M. Doborjiginidze, N. A. Graziansky et al., and A. I. Nesterova (2000). In turn, in patients with CHD in patients with chronic forms of CHD, there is an equivalent decrease in the daily excretion of catecholamines: A, NA, DA by 1.38; 1.41; 1.96 times, respectively ($p<0.001$), DOPA by 1.28 times ($p<0.05$) in relation to the control. In patients with CHD with chronic forms of CHD, inhibition of CAC activity is manifested by a decrease in the hormonal and neurotransmitter link, as well as a decrease in reserve capabilities due to a decrease in the release of DOPA ($p<0.05$) and dopamine ($p<0.001$). It is known that a decrease in the level of catecholamines in cardiovascular diseases can be a predictor of the development of arrhythmias, asystoles, and the threat of sudden death in stressful situations [10].

Currently, it is reliably known that the activation of free-radical peroxide processes underlies the pathogenesis of many diseases of internal organs. LPO processes cause the accumulation of oxidized LDL, which leads to microcirculation disorders [10]. From this point of view, the study of LPO processes in patients with AHS has become particularly interesting, since the main biochemical indicator of blood is an increase in LDL. It was found that in CHD and atherosclerosis, LPO increases. The intensity of LPO reflects the degree of metabolic disorders in the body [8]. Our results indicate an increase in LPO processes in CHD without CHD by 1.72 times ($p<0.001$), and the most pronounced intensification of LPO processes is observed in chronic forms of CHD, exceeding the control indicators by 2.16 times ($p<0.001$).

As is known, under the conditions of lipid peroxidation, the key enzyme of biogenic amine oxidation, MAO, can undergo a significant transformation of its catalytic properties, as a result of which its activity to monoamines decreases [7]. We studied the activity of MAO in healthy and AHS patients with CHD and without clinical manifestations of CHD. During observation, it was found that the functional activity of MAO in healthy and AHS patients with CHD and without clinical manifestations of CHD. MAO undergoes significant changes depending on the degree of manifestation of cardiovascular pathology. Thus, in patients with AHS without clinical forms of CHD, there is a decrease in MAO activity by 1.4 times ($p<0.001$). The lowest activity of the enzyme, which is 1.75 times ($p<0.001$) lower than that of the control group, is observed in patients with AHS with CHIBS, which confirms a qualitative violation of its catalytic properties.

The results obtained indicate that y patients with familial hypercholesterolemia clearly show a highly reliable, strong positive association of A and HA with the level of the cytokine IL-6 ($r=0.97$ and $r=0.94$; $p<0.01$). and

the cytokine IL-10 (r=0.93 and r=0.94; p<0.01). Therefore, cytokines are certainly the leading factors of impaired SAS activity, including in the case of AHS..

Thus, the data obtained revealed that the development and progression of CHD in AHS is accompanied by impaired functioning of the SAS. Increased sympathetic tone leads to a whole range of metabolic, trophic and hemodynamic changes, which is accompanied by an increased risk of cardiovascular accidents in patients with CHD. The results of our studies, to some extent, can show the important role of impaired SAS activity and LPO processes in the development of CHD and its complications in CHD.

In general, it can be assumed that among the important factors, the difference in the deterioration of the dynamics of neurohumoral indicators of interleukin status, lipid parameters, and the development of ischemic disease in AHS was associated with indicators that characterize non-specific inflammation and, above all, TNF-alpha and hf-CRP. This version is supported by the results of our study. Determination of lipid metabolism parameters, study of the state of CAC, MAO activity, LPO processes, and features of changes in cytokine status can provide additional information for early diagnosis of CHD and atherosclerosis in relatives with CHD, and assessment of the severity of CHD and atherosclerosis in CHD.

Conclusion

1. A comprehensive study of individuals with AHS without clinical manifestations of CHD showed an increase in the excretion of epinephrine, norepinephrine, dopamine, and DOPA by 26,5%, 14,4%, 9,3%, 4,5% accordingly, in relation to healthy people, which indicates the activation of the hormonal link of CAC, and therefore its early correction is necessary to prevent the development of coronary heart disease.
2. A comprehensive study of AHS patients with chronic forms of CHD revealed a decrease in the excretion of epinephrine, norepinephrine, dopamine, and DOPA by 27,7%, 29,3%, 48,8%, 22,0% accordingly, in relation to the control group, it indicates a decrease in the activity of the hormonal, mediator link and reserve capabilities of the CAC.
3. In the studied patients with AHCS, there is a significant decrease in MAO activity in relation to healthy ones, which indicates a qualitative change in the catalytic properties of the enzyme.
4. In patients with familial hypercholesterolemia, a highly reliable, strong positive association of A and NA with the level of the cytokine IL-6 is clearly traced (r=0.97 and r=0.94; p<0.01). and the cytokine IL-10 (r=0.93 and r=0.94; p<0.01).
5. A comparative assessmentof TNF-alpha and hf-CRP values in blood serum in healthy and AHS patients without clinical signs of CHD showed that in patients with AHS, the levels of TNF-alpha and CRP were 13.4±2.2 and 2.7±0.1, which is 1.76 times (p<0.001) and 2.5 times (p<0.001), respectively.0.001) more control parameters, more pronounced changes are observed in the group of patients with CHD with clinical signs of CHD.

Literature

1. Yezhov M. V., et al. Sergienko I. V., Rozhkova T. A., Kukharchuk V. V., Konovalov G. A., Meshkov A. N., Ershova A. I., Gurevich V. S., Konstantinov V. O., Sokolov A. A., Shcherbakova M. Yu., Leontieva I. V., Bazhan S. S., Voevoda M. I., Shaposhnik I. I. Russian recommendations for diagnostics and treatment of familial hypercholesterolemia // Eurasian Journal of Cardiology. 2017. No. 2. pp. 7-12.
2. Yezhov M. V., Bliznyuk S. A. Register of patients with familial hypercholesterolemia and patients with very high cardiovascular risk with insufficient effectiveness of lipid-lowering therapy (RENAISSANCE)

Eurasian Journal of Cardiology. 2019; No. 24-5, pp. 7-13.
3. Meshkov A. N., Stambolsky A.V., Nikitina L. N. et al.Genetic risk factors for the development of coronary heart disease in patients with familial hypercholesterolemia. Kardiologiya 2005; 7: 10-15.
4. KeesHovinghG., DavidsonM.H., KasteleinJ.P, O'KonorA.M. Diagnosisand
5. treatment of familial hypercholesterolaemia. European Heart Journal. 2013. № 34.
6. P. 962–971. DOI: 10.1093/eurheartj/eht015.
7. Singh S., Bittner V. Familial hypercholesterolemia-epidemiology, diagnosis, and
8. screening. Curr Atheroscler Rep. 2015. No.17(2). R.482. DOI: 10.1007 / s11883-014-
9. 0482-5.
10. Michael D.S., Sergio F. Taking a look under the hood. Journal of Clinical
11. Lipidology. 2018. № 5. P. 3–6. DOI: 10.1016/j.jacl.2018.05.020
12. Schwartz J., Padmanabhan A. Aqui N., Balogun R.A., Delaney M., Dunbar N.M., Witt V., Wu Y., Shaz B.H. Guidelines on the Use of Therapeutic Apheresis in
13. Clinical Practice-Evidence- Based Approach from the Writing Committee of the
14. American Society for Apheresis: The Seventh Special Issue. J. Clin Apher. 2016
15. Jun; 31(3): 149–62. DOI: 10.1002/jca.21470.
16. Kees Hovingh G., Davidson M.H., Kastelein J.P, O'Konor A.M. Diagnosis and
17. treatment offamilial hypercholesterolaemia. European Heart Journal. 2013. № 34.
18. P. 962-971. DOI: 10.1093 /eurheartj/eht015.
19. 9. Lankin V. Z., Vikhert A.M., Tihase A. K. Free-radical processes in the presence of
20. diseases of the cardiovascular system. Kardiologiya 2000; 7: 48-61
21. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376 (18):1713-22.doi:10.1056/NE