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Clinical and Laboratory Features of Coronary Heart Disease in Patients with Aspirin Resistance

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Abstract **Purpose.** To determine the frequency of aspirin resistance in patients with coronary heart disease and evaluate the risk factors for the developement aspirin resistence in patients with coronary heart disease. **Material and methods.** 88 patients were enrolled in the study with stable forms of coronary heart disease, who received a standard dose of aspirin 75 mg/day for a long time. Platelet aggregation was measured using a laser analyzer, and adenosine diphosphate was used as an inducer. All statistical analysis were performed SPSS software. **Results.** 35.2% of patients who took aspirin at a standard dose of 75 mg / day were resistant to aspirin. The average degree of platelet aggregation with 5.0 mmol of ADP was 79.4% in patients with resistant to aspirin. Patients with aspirin resistance were significantly more likely to have a history of myocardial infarction than aspirin-sensitive individuals. There were a correlation between lipid disorders and the functional state of platelets. The most significant negative correlation of the platelet aggregation index was determined in relation to the level of cholesterol ($r = -0.41$) and triglycerides ($r = -0.43$). Possible risk factors for the development of ASA resistance were: female gender, old age, obesity, hypercholesterolemia and hyperglycemia, since patients with aspirin resistance tended to have higher cholesterol and glucose levels ($p<0.05$). **Conclusion.** Aspirin resistance was more common in patients with coronary heart disease taking aspirin over 5 years, the elderly and in women. Possible risk factors for developing ASA resistance are old age, female gender, obesity, and hypercholesterolemia.

Keywords Aspirin, Aspirin resistance, Coronary heart disease, Platelet aggregation

1. Introduction

Currently, it is proved that the appointment of antiplatelet drugs for the primary and secondary prevention of acute cardiovascular events is a mandatory component of the pharmacotherapy of CHD and is included in the clinical recommendations of different levels [2,6,7,9]. Acetylsalicylic acid (aspirin) is considered to be the only disaggregate whose clinical efficacy has been proven by numerous clinical studies [7,8,9].

In recent years, it has been noted that in a number of patients, aspirin has less pronounced antiplatelet activity. This phenomenon is known as aspirin resistance. According to different authors, the frequency of determining aspirin resistance varies significantly – from 5.2% to 57% [1]. These patients appear to have a poorer prognosis than patients with clear, ASA-dependent inhibition of platelet function [3]. An analysis conducted in Cleveland clinic's revealed a correlation between aspirin resistance and clinical outcomes, and also revealed that patients with aspirin resistance, which was studied using an express platelet functional state analyzer, are more than three times more likely to develop ischemic complications in the future (death, stroke or myocardial infarction) [5].

Resistance to aspirin is defined as: the inability of aspirin to protect the patient from thrombotic complications; to prolong the bleeding time; to suppress the biosynthesis of THA2; to suppress platelet function in one or more in vitro tests. The problem of resistance to antiplatelet drugs is fundamental in its significance, since it creates prerequisites for the individualization of preventive therapy and the formation of more effective methods for preventing the disease. [4].

The prevalence of aspirin resistance and its clinical significance are poorly understood. Patients with chronic coronary heart disease take aspirin for years, but do not know the effectiveness of this drug, and it is not always possible to determine the effectiveness of antiplatelet agents using laboratory tests.

The purpose of this study was to study the prevalence of aspirin resistance and the factors influencing aspirin resistance in patients with coronary heart disease who take aspirin for a long time.

2. Materials and Methods

The study included 88 patients aged > 18 years with a diagnosis of CHD stable angina pectoris (SAP) of functional classes II-III (FC). The patients were treated in the

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cardiology department of the Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation. The diagnosis of CHD in the form of a clinical form of SAP II-III FC, established according to European recommendations [2].

All patients received standard therapy: antithrombotic, antihypertensive, antianginal drugs, statins. As an antiplatelet agent, ASA (tablets coated with an intestinal-soluble coating) was prescribed at a dose of 75 mg. All patients underwent physical examination, clinical and laboratory methods of investigation (general blood analysis, biochemical blood analysis, blood lipid spectrum and coagulogram), platelet aggregation and functional diagnostics (ECG, EchoCG).

The study of platelet aggregation in platelet-rich citrate plasma by the Born and O'Brien method was performed on a two-channel laser analyzer of platelet aggregation Alat-2 Biol, with computer processing according to the AGGR program. Solutions of adenosine diphosphate (ADP) with final concentrations of 0.1, 1.0, and 5 µg/ml were used as aggregation inducers. The normal limits of the activity of the platelet aggregation process with the addition of 5.0 mmol of ADP are 25-72%. Statistical processing of the study data was carried out using the SPSS 18.0 software.

3. Results

The study included 88 patients (40 men and 48 women), the average age was 66.4 (45.3—78.4) years. Table 1 shows the characteristics of patients with CHD.

According to the results, increased platelet aggregation was detected in more than one in three patients (31 (35.2%)). Studying the nature of the antiplatelet response, it was found that in patients with increased platelet aggregation, changes in spontaneous aggregation and under the influence of an inducer at a concentration of 5.0 mmol were most often recorded both with and without ASA.

The largest number of patients showed a combined increase in spontaneous and induced aggregation at an inducer of ADP concentration of 5.0 micromol (35.4%) (Fig. 1). An isolated increase in spontaneous aggregation alone was detected in 25.8% of cases when taking ASA. An increase in platelet aggregation with a combination of 0.1 and 1.0 inducer concentrations with 5.0 mmol inducer of ADP was detected in 6.4% of patients taking ASA. Isolated increase in platelet aggregation under the influence of minimal concentrations of the inducer was detected much less frequently.

Table 1. Clinical and anamnestic characteristics of patients with coronary heart disease

Parameters	n (%)
patients with CHD	88
Age, years	66.4 ± 7.3
Men, pers	40 (45,4%)
Women, pers	48 (54,5%)
Obesity (BMI30)	52 (59%)
Smoking	30 (34%)
Alcohol	11 (12.5%)
Stable angina pectoris II FC	68 (77.2%)
Stable angina pectoris III FC	20 (22.7%)
Post-infarction cardiosclerosis	47 (53.4%)
Atherosclerosis	51 (57,9%)
Hypertension	72 (81.8%)
Atrial fibrillation	9 (10.2%)
CHF	43 (48.8%)
Type II diabetes	57 (64.7%)

Note: n is the number of patients.

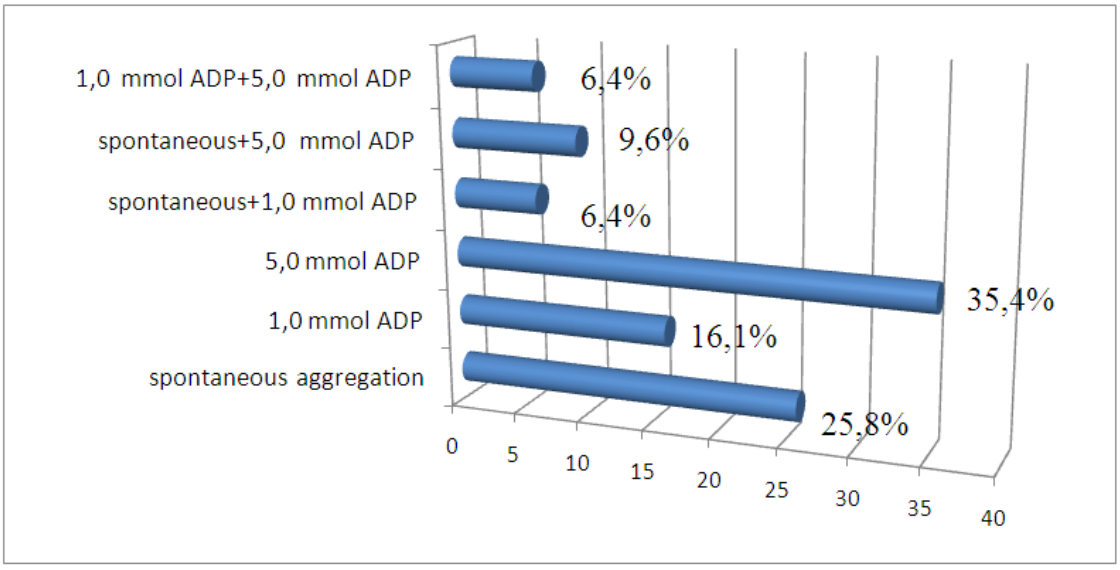

Figure 1. Distribution of the increased aggregation response depending on the concentration of the inducer in patients with CHD receiving ASA preparations

It was noted that when exposed to ADP at a concentration of 0.1 mmol, the percentage of light transmission did not differ from the norm in patients receiving ASA, despite the presence of spontaneous hyperaggregation or increased platelet activity when exposed to higher concentrations of the inducer.

Patients with SAP were divided into 4 groups according to the prescription of taking ASA. Group 1 consisted of patients who did not receive aspirin, the second group consisted of patients taking aspirin up to 1 year, the third group consisted of patients taking aspirin from 1 year to 5 years, and the fourth group included patients taking aspirin over 5 years.

The results of the study are presented in Table. 2. Analysis of ADP-induced platelet aggregation showed that when exposed to ADP in all concentrations used in the group of patients with CHD taking aspirin for more than 5 years, the degree of platelet aggregation was greater than in the other groups. At the same time, significant changes were observed in the indicators of the degree of spontaneous platelet aggregation and induced aggregation with the concentration of inductor 5.0 mkmoladf ($p<0.05$).

With increasing age, there was an increase in the functional activity of platelets in patients taking ASA drugs (Table 3), which was statistically significant against the background of ADP use at a concentration of 5.0 mmol.

By gender, the study of the gender characteristics of platelet aggregation in patients with CHD showed that women who received antiplatelet therapy predominate (54.3%) (tab. 4) and assessing the frequency of increased platelet aggregation, the prevalence of women compared to men was also established (73.4% and 26.9%).

As a result of the study, it was found that obese patients with CHD have higher spontaneous aggregation and ADP-induced platelet aggregation. It is proved that the high metabolic activity of visceral adipose tissue leads to the activation of lipid peroxidation, promotes the progression of dyslipidemia and endothelial dysfunction, which, in turn, triggers the cascade of thrombosis.

Table 2. Indicators of spontaneous and ADP-induced platelet aggregation in patients with ischemic heart disease taking aspirin for a long time

Indicator	Degree of aggregation, %			
	Patients who did not receive aspirin	Patients taking aspirin up to 1 year	Patients taking aspirin from 1 year to 5 years	Patients taking aspirin over 5 years
Spontaneous aggregation	2,03	1,08	1,6	2,24*
0,1 Mmol ADP	6,4	3,4	5,4	7,8
1.0 mmol ADP	15,7	6,5	12,8	31,8
5.0 mmol ADP	58,2%	43,2%	52,2%	68,8%*

*P<0.05 compared to the original data

Table 3. Platelet aggregation in patients with CHD with and without aspirin resistance, depending on the risk factor-age, M±SD

Aggregation indicators	Young and middle, n=33 (37.5%)	Elderly and senile, n=55 (62.5%)	p
Spontaneous aggregation, rel. units	1,61±0,13 95% CI 1,45-1,74	1,72±0,4 95% CI 1,50-1,87	0,46
0,1 Mmol ADP rel. units	2,14±0,11 95% CI 1,72-2,38	2,33±0,17 95% CI 2,09-2,65	0,37
1.0 mmol ADP rel. units	2,96±0,4 95% CI 2,35-3,71	3,4±0,18 95% CI 2,79-3,86	0,24
5.0 mmol ADP,%	21,44±2,32 95% CI 15,2-27,6	29,7±2,38 95% CI 25,7-34,5	0,047*

Note: n is the number of patients, CI is the confidence interval, and p is the significance of the differences.

Table 4. Parameters of platelet aggregation in patients with CHD on the background of antiplatelet therapy, depending on gender, M±SD

Aggregation indicators	Men (n=40)	Women (n=48)	p
Spontaneous aggregation, rel. units	1,54±0,2 95%CI 1,35-1,78	2,81±0,3 95% CI 1,7-2,06	0,014*
0,1 Mmol ADP rel. units	2,11±0,18 95% CI 1,71-2,6	2,16±0,12 95% CI 2,5-2,8	0,27
1.0 mmol ADP rel. units	2,62±0,27 95% CI 2,17-3,26	3,85±0,1 95% CI 3,7-3,5	0,017 *
5.0 mmol ADP,%	21,3±2,9 95% CI 17,1-26,0	29,85±2,26 95% CI 24,1-34,0	0,047*

Note: n is the number of patients, CI is the confidence interval, and p is the significance of the differences.

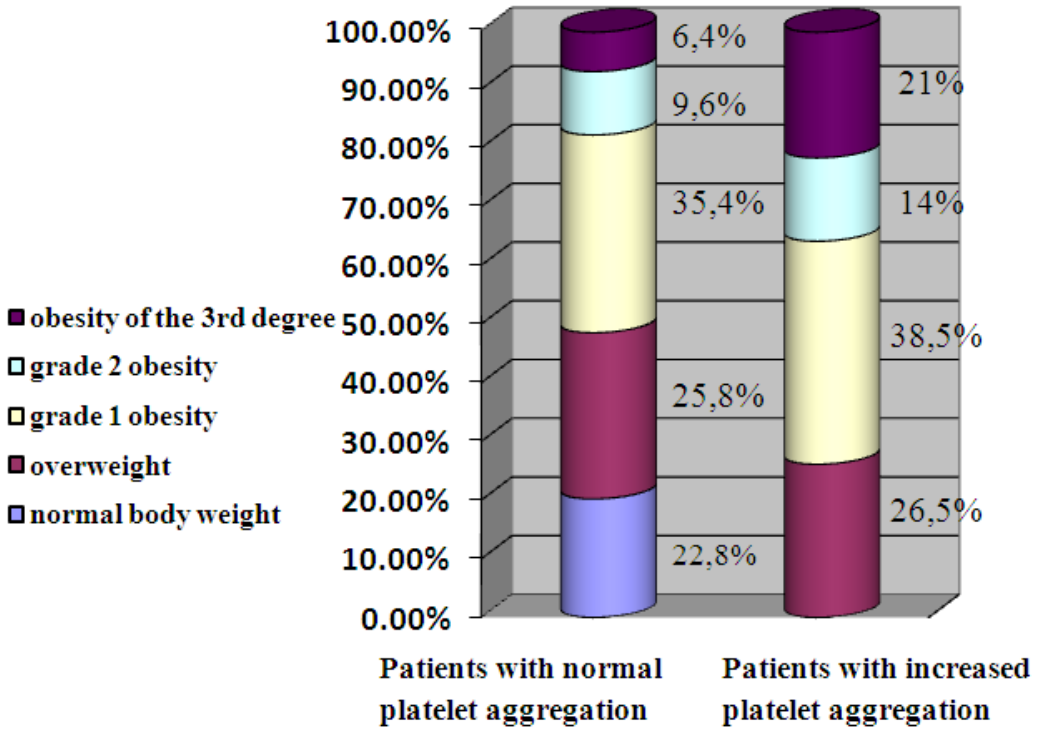

Figure 2. Distribution of patients with normal and increased platelet aggregation depending on body weight

Table 5. Laboratory parameters of patients with CHD with and without aspirin resistance M±SD

Indicator	Gr. ASA resistant (n=31)	Gr. ASA sensitive (n=57)	P
XC (mmol/l)	*6,8±1,32	5,1±1,22	0,04*
TG (mmol/l)	*2,51±1,6	1,97±1,7	0,04*
low-density lipoproteins (mmol/l)	4,76±1,4	4,12±1,5	0,46
very low-density lipoproteins (mmol/l)	0,95±1,6	0,88±1,2	0,72
high-density lipoproteins (mmol/l)	0,84±1,0	0,96±1,4	0,74
Red blood cells	4,73±0,44	4,84±0,49	0,88
Platelets	261,9±61,6	279,9±67,3	0,82
Blood glucose	8,7±3,6	5,6±4,3	0,05*

* *P<0,05* – compared to the control

Weight gain is associated with an increase in the prevalence of other cardiovascular risk factors.It can be assumed that the platelet aggregation function depends on the complex of metabolic disorders that accompany obesity. In the group of patients with increased platelet aggregation, the body mass index in 100% of cases exceeded the norm: in 38.5% of cases - obesity of the 1st degree, 14% - obesity of the 2nd degree, 21% - obesity of the 3rd degree, and in 26.5% - excess body weight (Fig. 2). Patients with normal weight in this group were not registered. In all cases, the abdominal obesity was worn by the character.

Given the close relationship between lipid metabolism and functional state of platelets, we analyzed the possibility of development of resistance to ASA, depending on the lipid profile (table. 5). It was found that patients with higher platelet aggregation values of total cholesterol, lipid profile (triglycerides, atherogenic lipoproteins) exceeded those indicators in the group of patients with normal aggregation.

The most significant negative correlation of the platelet aggregation index was determined in relation to the cholesterol level (r = -0.41) and triglycerides (r = -0.43). It is possible that a violation of lipoprotein metabolism contributes to a change in the functional activity of platelets due to the rearrangement of the lipid structure of the platelet membrane, which is accompanied by an increase in their ability to respond to aggregation inducers.

Thus, as can be seen from the results of our study, an increase in the concentration of proatherogenic lipoproteins is observed in patients with CHD, which corresponds to the data from the literature.

Differences in the number of patients who had suffered a myocardial infarction were revealed. In the group of ASA-sensitive patients, 31 out of 57 patients had a history of Q — forming myocardial infarctions, and in the group of ASA-resistant patients-in 29 out of 31 (p=0.037).

4. Conclusions

1. Aggregation aspirin resistance was observed in 1/3 of patients with ischemic heart disease who took aspirin for a long time.
2. Patients with ASA resistance were significantly more likely to have a history of myocardial infarction than aspirin-sensitive individuals.
3. Possible risk factors for the development of resistance to ASA are: old age, female gender, obesity and hypercholesterolemia.

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