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THE ROLE OF INFLAMMATORY REACTIONS AND HEMORHEOLOGICAL INDICATIONS IN PATIENTS WITH RESTENOSIS AFTER CORONARY ANGIOPLASTY, OPTIMIZATION OF TREATMENT

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SUMMARY

Purpose. The aim of the trial was to study the importance of immuno-inflammatory processes and hemo-rheological changes in patients suffering from stable coronary heart disease after coronary angioplasty and stenting, as well as establishing the clinical effect of treatment optimized with anti-inflammatory drugs and immune-correctors.

Material and methods. The study included 103 patients in total and 64 patients with an implanted stent. Within 2-28 months after stent implantation, an angiographic study was performed with the definition of a coagulogram, C-reactive protein (CRP), fibrinogen, and pro-inflammatory cytokines – tumor necrosis factor (FNA-α), interleukins (IL), IL-6, IL-8 in the serum of patients with coronary artery disease.

Results. After coronary angioplasty and stenting in patients with coronary artery disease, the average concentrations of CRP and cytokines were significantly higher compared with both the control group and the group without restenosis. This indicator in the groups with and without restenosis was 16.4±1.2 (intragroup variation 6-36) mg/L and 6.8±0.4 (intragroup variation 5-10) mg/L, respectively; $p<0.001$. And from cytokines, the concentration of IL-6 in groups with and without restenosis was respectively 3.5+0.2 and 18.7+3.1 ($p<0.01$). In the correlative analysis in the group with restenosis, the expected close relationship between TNF-alpha and IL-6 is equal to $r = 0.707$, $p<0.01$, between CRB and IL-6, equal to $r = 0.575$, $p<0.01$, and between TNF-alpha and IL-8, equal to $r = 0.610$, $p<0.05$.

Keywords: *immuno-inflammatory reactions, cytokine imbalance, inflammatory mediators, C-reactive protein, fibrinogen, stent restenosis.*

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INTRODUCTION

According to the data of various research workers, a damage to intima, mural thrombus formation and further thrombogenic subendothelial layer exposure could be described as initial mechanism of coronary artery restenosis development for patients with ischemic heart disease undergone endovascular intervention [1], as the development of inflammatory response into a damage or implantation of a stent and expression of the adhesion receptors [2]. According to the data of two widely randomized studies – BENESTENT and STRESS [3,4,5], the frequency of the restenosis development after stent placement remains steadily high and varies within 22% to 31%. From the today's point of view, more clear and distinct description is given in the article titled "A monk's prayer: O Lord what is the answer to in-stent restenosis?", printed in the European Heart Journal: "the in-stent restenosis is an iatrogenic disease affected in 2001 over 200,000 patients all over the world" [6].

The proposed coronary in-stent restenosis forecasting method is based on the local response development, which activates persistent inflammation leading to increased expression of the immune competent cells, including cytokines, monocytes, macrophages, endotheliocytes, T-lymphocytes, damaged as a result of the loss of endothelial layer integrity against a background of existing hypercytokinaemia, reflecting chronical immune inflammation in case of atherosclerosis and during angioplasty and/or stent placement into a stenosed target coronary artery [7]. The role of the inflammation mediators for pathogenesis of

the stenotic coronary atherosclerosis is actively discussed by cardiologists, cardiovascular surgeons and pathophysiologists. However, certain mechanisms of atherosclerotic damage to a coronary bed remain poorly clear, despite having proven a significant increase of local cytokines generation associated with hyperplasia of neointima inside a stent and excessive activation and further hyperproliferation of neointimal apoptosis after the stent placement into a coronary artery (CA) during the experiment [8,9]. All of this stimulates consistent cell-proliferative responses development in the form of hypersensitive responses as developed in early periods, both in the implanted stent locus immediately after intervention, and after endovascular revascularization, thus increasing the risk of the coronary restenosis development.

MATERIALS AND METHODS

The study covered the patients of the D.M. Abdullaev Cardiology Research Institute, with the coronary stent implanted earlier and the repeated coronary angiography planned for any reason. The criteria for being included into the study were stable effort angina of the functional classes II and III, as well as restenosis of one or more coronary artery (vessel clearance narrowing by more than 51% in comparison with the original size) during 2-24 months and more after the stent placement. The criteria for the patients to be included into the study were clinical developments of rest angina (unstable heart angina) at the moment of getting to the intensive care unit (with duration of at least 10, but not more than 30 minutes); effort angina (in case of efforts not resulted in angina in the past); ST segment depression (over 0.1 mV) in the electrocardiogram and/or increase of the number of attacks with transient transformations in the form of the T-peak inversion in two or more branches without creating new Q-peaks on the ECC.

The reasons for a repeated angiography for the patients were either ischemia proven by the invasive tests (myocardial perfused scintigraphy or treadmill testing) or the functional class III-IV angina. After clinical, angiographical and laboratory analyses, the patients with proven in-stent restenosis were included in the restenosis group (angiographic narrowing of more than 51% were recognized as the restenosis group) (n=44). 44 in-stent restenosis patients were divided in 2 groups. The group 1 patients (n=20) got the first aid and traditional therapy in line with the disease severity. And the group 2 patients (n=24), in addition to the basic therapy, were provided with immunomodulators (SELVERIN 200 mg, 1.5 month) and selective anti-inflammatory (cyclooxygenase blocking agents 2 – Meloxicam 15 mg, 1 per day, 2 months) medicines. The patients with open angiographic stents were included into a control group. The study did not cover the patients with acute coronary syndrome within 3 months before the angioplasty. The criteria for being included also were the in-stent thrombosis, any inflammatory disease in the medical history which has been cured by using anti-inflammatory and immune suppressive medicines, excluding aspirin, within the last 6 months. Clinical characteristic of the patients is given in Table 1.

Laboratory Investigation. Blood samples were taken within 2-28 months after the placement of stent, from all patients with ischemic heart disease. The studied inflammation markers and mediators were C-reactive protein (CRP), differential white blood cell count, as well as hemoreologic values – INR, prothrombin time, fibrinogen, and of cytokines – tumor necrosis factor (TNF-α), interleukin (IL) IL-6.

The number of biologically active molecules was determined by immunoenzymometric method.

34 patients were implanted with 1 stent, 24 patients with 2 and 6 patients with 3 stents. After the stent placement, there was no significant difference between the groups with and without restenosis in terms of using medicines, including b-blocking agents, aspirin, statin, clopidogrel.

RESULTS

As it can be seen from the Table, the patients with angina after the stent-placement had the fibrinogen of 4.20+0.11 (the intra-group variation is 3.8-6). And within the open stent control group (without restenosis) it was 3.47+0.08 (the intra-group variation is 2.9-4.4).

The fibrinogen of 13 patients (65.0%) within the group 1 before curing was higher than the normal value, and of the rest of 7 patients (35.0%) it was within the normal range ($\chi 2$=13.30, p<0.001). The results obtained for the patients with angina after the stent placement show a statistically significant fibrinogen increase. Such an increase was 1.2 time higher than for the control group (p<0.001). And after curing the fibrinogen was 4.28+0.08 (the intra-group variation is 3.6 and 4.8), demonstrating no statistical difference in comparison with the value before curing. Also, for 15 patients (75%) it was higher than the normal value, for 5 patients (25%) it was within the normal range ($\chi 2$=17.60, p<0.001). It was staying 1.2 time higher in comparison with the control group (p<0,001).

The fibrinogen of 15 patients (62.5%) within the group 2 before curing was higher than the normal value, and of the rest of 9 patients (37.5%) it was within the normal range ($\chi 2$=13.20, p<0.001). This value was 1.2 time higher in comparison with the control group (p<0.001).

After curing the fibrinogen, being 3.62+0.05 (the intra-group variation is 2.9 and 4.1), was p<0.001 in comparison with the value before curing, decreased 1.2 time and demonstrating no statistical difference in comparison with the control group. Also for 1 patient (4.2%) it remained higher than the normal value, and for 23 patients (95.8%) it was within the normal range ($\chi 2$=0.35). In comparison with the value of the group undergone standard

Table 1. Hemorheologic values before and after curing

Parameters	Group 1 (n=20)		Group 2 (n=24)		Control group (n=20)
	Before	After	Before	After	
Fibrinogen, g/l	4,20+0,11 ***	4,28+0,08***	4,22+0,11***	3,62+0,05^^^###	3,47+0,08
INR	1,21+0,04***	1,20+0,04***	1,15+0,01***	1,28+0,04***^^	1,57 +0,07
Prothrombin time (s)	12,1+0,4**	11,8+0,3***	12,0+0,1***	12,7+0,2*##^^	13,3+0,1
Erythrocyte sedimentation rate (mm/hour)	22,9+3,5 **	18,9+2,1***	23,1+1,9***	9,3+0,4^^^###	10,1+0,8

*For the control group * – p<0.05, **p<0.01, ***p<0.001*
For the group of comparison # – p<0.05, ## – p<0.01, ### – p<0.001
For the same group before curing ^ – p<0.05, ^^ – p<0.01, ^^^ – p<0.001

therapy, the fibrinogen decrease after curing (group 1) with the difference of p<0.001.

INR. According to the Table given above, there was no statistically reliable difference between the groups before curing in terms of the INR value. For the patients with angina after the placement of stent, this value before curing was 1.21+0.04 (the intra-group variation 1.11-1.86). This value was 1.3 time lower in comparison with the control group, by differing from the control group's value as p<0.001. In the control group it was 1.57+0.07 (the intra-group variation 1.06-1.77).

In the group 1 the INR of 1 patient (5.0%) before curing was deviated from the normal value, and for 19 patients (95.0%) it was within the normal range (χ2=13.30, p<0.001). The obtained results show that the majority of patients with angina after the stent placement had INR within the normal range, while in comparison with the control group such a value was 1.3 time lower (p<0.001). And after curing the INR, being 1.20+0.04 (the intra-group variation is 1.06 and 1.77), had changed without statistical significance in comparison with the value before curing. Also for 2 patients (10%) it deviated from the normal value, and for 18 patients (90%) it was within the normal range (χ2=10.67, p<0.001). However, It was staying 1.3 time lower in comparison with the control group (p<0,001).

The INR within the group 2 (provided with the anti-inflammable medicines) was 1.15+0.01 before curing. Despite the INR of the majority of the patients was within the normal range in comparison with the control group, such a value was 1.4 time lower (p<0.001). And after therapy the INR, being 1.28+0.04 (the intra-group variation is 1.11 and 2.05), has demonstrated a statistically significant growth in comparison with the value before curing (p<0.01). Also for 5 patients (20.8%) it deviated from the normal value, and for 19 patients (79.2%) it was within the normal range (χ2=8.80, p<0.01). INR value in this group, provided with the optimized therapy, before and after curing was 1.4 and 1.2 times lower in comparison with the control group, respectively, with the difference of p<0.001. In comparison with the standard therapy group, no difference was noted.

TNF-a. For the patients with angina after stent placement TNF-a was 4.4 times higher in comparison with the control group, being 13.6+2.0 (within the control group 3.1+0.2) before curing for the patients provided with the standard therapy (p<0.001). The TNF-a of 18 patients (90.0%) within the group 1 before curing was higher than the normal value, and of the rest of 2 patients (10.0%) it was within the normal range (χ2=29.19, p<0.001). The results obtained for the patients with angina after the stent placement show a statistically significant TNF-a increase. Such an increase was 4.4 time higher in comparison with the control group (p<0.001). And after curing the TNF-a, being 10.9+1.4 (the intra-group variation is 2.1 and 27), had decreased without statistical significance in comparison with the value before curing. It was staying 3.6 times higher in comparison with the control group (p<0.001).

Within the group 2 the TNF-a being 12.9+1.6 before curing, was higher than the normal value for 24 patients (100%). This value was 4.2 time higher in comparison with the control group (p<0.001). And after curing the TNF-alpha, being 5.9+0.3 (the intra-group variation is 3.1 and 8,5), had decreased 2.2 times in comparison with the value before curing (p<0.001). It was staying 1.9 time higher in comparison with the control group (p<0.001). And in comparison with the value after curing within the group of patients provided with the standard therapy, it was decreased as p<0.001.

The correlation analysis has shown the expected close intercorrelation between the TNF-alpha and IL-6 as r=0.707, p<0.01, and between TNF-alpha and IL-8 as r=0.610, p<0.05.

IL-6. The patients with angina after the stent placement provided with the standard therapy, of cytokines the IL-6, being 19.3+4.8 (within the control group 3.5+0.2) before curing, exceeded the control group's value 5.6 times (p<0.01). The IL-6 of 14 patients (70.0%) within the group 1 before curing was higher than the normal value, and of the rest of 6 patients (30.0%) it was within the normal range (χ2=18.57, p<0.001). The results obtained for the patients with angina after the stent placement show a statistically significant IL-6 increase. Such an increase was 5.6 time higher in comparison with the control group (p<0.01). And after curing the IL-6, being 14.6+3.3 (the intra-group variation is 2.7 and 68), had decreased without statistical significance in comparison with the value before curing. Also for 8 patients (40%) it was higher than the normal value, and for 12 patients (60.0%) it was within the normal range (χ2=7.66; p<0.01). It was staying 4.2 times higher in comparison with the control group (p<0.01).

The IL-6 of 19 patients (79.2%) within the group 2 before curing, being 18.1+4.1, was higher than the normal value, and of the rest of 5 patients (20.8%) it was within the normal range (χ2=24.73, p<0.001). This value was 5.3 time higher in comparison with the control group (p<0.01). And after curing the IL-6, being 6.8+0.4 (the intra-group variation is 4.4 and 11.9), had decreased 2.7 times in comparison with the value before curing (p<0.01). Also for 1 patient (4.2%) it continued remaining higher than the normal value, and for 23 patients (95.8%) it was within the normal range (χ2=0.01). It was staying 2 times higher in comparison with the control group (p<0,01). And in comparison with the value of the group of patients undergone standard therapy, the decrease after curing had the difference of p<0.05. The correlation analysis carried out for the patients between IL-6 and CRP has shown expected close intercorrelation as r=0.575, p<0.01, and for fibrinogen it was r=0.316, p<0.05.

Table 2. Level of immunological values before and after curing

Parameters	Group 1 (n=20)		Group 2 (n=27)		Control group (n=20)
	Before	After	Before	After	
TNF-alpha pg/ml	13,6+2,0***	10,9 +1,4***	12,9+1,6***	5,9+0,3***###^^^	3,1+0,2
IL-6 pg/ml	19,3+4,8**	14,6+3,3**	18,1+4,1**	6,8+0,4**^^#	3,5+0,2
IL-8 pg/ml	9,9+1,8***	7,1+1,2***	10,4+ 1,6***	4,3+0,4***^^#	2,2+0,1
CRP (mg/l)	17,6+2,0***	13,0+1,1***	17,3+1,5***	7,0+0,4^^^###	6,8+0,4

*For the control group * – p<0.05, ** – p<0.01, *** –p<0.001*
For the group of comparison # – p<0.05, ## – p<0.01, ### – p<0.001
For the same group before curing ^ – p<0.05, ^^ – p<0.01, ^^^ – p<0.001

IL-8. For the patients with angina after the placement of stent provided with the standard therapy, of cytokines the IL-8, being 9.9+1.8 before curing, was 4.5 times higher in comparison with the control group ($p<0.001$) Thus, IL-8, being 2.2+0.1 within the control group, was varying within group from 1.1 to 3.2. And after curing the IL-8, being 7.1+1.2 (the intra-group variation is 0.2 and 22.3), had decreased 1.4 times in comparison with the value before curing. It was staying 3.2 times higher in comparison with the control group ($p<0.001$).

IL-8, being 10.4+1.6 within the second group before curing, was 4.7 times higher in comparison with the control group ($p<0.001$). And after curing the IL-8, being 4.3+0.4 (the intra-group variation is 1.1 and 8.3), had decreased 2.4 times in comparison with the value before curing ($p<0.001$). In comparison with the value of the group of patients undergone standard therapy, after curing the difference was $p<0.05$. It was staying 1.9 time higher in comparison with the control group ($p<0.001$).

CRP. According to the Table, the CRP for the patients with angina after the stent placement within the group provided with the standard therapy, was 17.6+2.0 (the intra-group variation of 6-36). For the control group patients it was 6.8+0.4 (the intra-group variation 5-10). The results obtained for the patients with angina after the stent placement show a statistically significant CRP increase. Such an increase was 2.6 time higher in comparison with the control group ($p<0.001$). And after curing the CRP, being 13.0+1.1 (the intra-group variation is 6 and 22), had decreased 1.4 time in comparison with the value before curing. Also for 17 patients (85%) it was higher than the normal value, and for 3 patients (15%) it was within the normal range ($\chi2=10.23$; $p<0.01$). It was staying 1.9 time higher in comparison with the control group ($p<0.001$).

The CRP of 23 patients (95.8%) within the group 2 before curing, being 17.3+1.5, was higher than the normal value, and of the rest of 1 patient (4.2%) it was within the normal range ($\chi2=18.21$, $p<0.001$). This value was 2.5 time higher in comparison with the control group ($p<0.001$). And after curing the CRP, being 7.0+0.4 (the intra-group variation is 6 and 12), had decreased 2.5 times in comparison with the value before curing ($p<0.001$). Also, for 6 patients (25.0%) it was higher than the normal value, for 18 patients (63.0%) it was within the normal range ($\chi2=0.14$). This had not a statistically significant difference in comparison with the control group. In comparison with the value of the group of patients undergone standard therapy, the decrease after curing was 1.9 time ($p<0.001$).

DISCUSSION

The study performed in Switzerland, when 10 000 patients were under observation for 8 years, it was declared, that fibrinogen is a strong predictor of death for the patients of both genders, in relation with lethal and non-lethal ischemic heart disease, and for any other reason (124). The study performed by Goffmeister et al. has shown that patients with unstable heart angina had higher fibrinogen value in comparison with the control group. The same study determined a significant association between the morphological staging of the coronary stenosis complex according to ACC/AHA for the patients with unstable heart angina (126). This value has been confirmed one more time in our study (Table 1).

Therefore, the anti-inflammable IL-6 and TNF-alpha after the placement of stent into the coronary artery are the cytokine concentration predictors, and assessment of the acute phase mediators dynamics in combination with the clinical and angiologic monitoring of the coronary blood circulation is the indication of clinical in-stent restenosis. We have justified a positive clinical effect of immunomodulating and anti-inflammable curing provided in addition to the standard therapy in terms of the pathogenesis.

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