Correction of aggregation level of basic regular blood elements in patients with hypertension and dyslipidemia receiving rosuvastatin and non-medicinal treatment

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ABSTRACT

Background: In the treatment of patients with hypertension and dyslipidemia, great attention has been devoted to hypolipidemic diet, graduated exercise and statins. Accordingly, a complex application of non-medication and statins to those patients is concerned in weakening of regular blood elements' aggregative ability. This study aims to establish the complex impact of rosuvastatin and nonmedicinal therapy on aggregative features of regular blood elements in patients with arterial hypertension and dyslipidemia.

Materials and Methods: There were 61 patients with grade I-II of hypertension, risk 3 with dyslipidemia of IIb type. All the patients were prescribed rosuvastatin, hypolipidemic diet, and graduated exercise. Enalapril 10 mg twice a day was given for hypotension. Registration of clinical and laboratory indices was made in 6, 12, 18, 52 and 104 weeks of therapy. Biochemical, hematological, and statistical methods of investigation were applied. There were 26 healthy volunteers as a control group.

Results: This study shows a surplus aggregation of erythrocytes (aggregates' quantity rose to 44.4%), platelets (with ADP on 74.5%; with collagen - on 48.2%) and neutrophils (with lectin on 55.8%; with phytohemagglutinin - on 38.2%). During 104 weeks of therapy, it suggested a positively influenced lipid composition and level of lipid peroxidation in plasma as well as regular blood elements taking the given indices on the control level for 6 weeks. Fulfilled therapy show a normalized erythrocytes' aggregative abilities (aggregates' quantity decreased on 44.4%), platelets' aggregation (inhibited with ADP on 74.8%, with collagen - on 47.8%), and neutrophils (aggregation weakened with lectin on 55.8%, with phytohemagglutinin - on 38.2%) during 6 weeks. Reaching results were kept in patients until the end of the investigation.

Conclusion: Rosuvastatin intervention give normalizes lipid composition and level of lipid peroxidation in plasma as well as regular blood elements for 6 weeks of study. In addition, it is also lowering erythrocytes' aggregative abilities as well as platelets and neutrophils during for 6 weeks of therapy.

Keywords: hypertension, dyslipidemia, rosuvastatin, non-medication, aggregative activity, regular blood elements.

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INTRODUCTION

Arterial hypertension (AH) is one of the most significant health issues among cardiovascular diseases. The high frequency of AH complications is additionally increased in the case of its combination with different metabolic abnormalities including dyslipidemia (D). Evident danger of AH with D combination is determined by the progression of atherosclerosis strengthening on its background. It significantly raises the risk of thromboses' development and sharply worsens long-term prognosis.

It becomes clear that AH and D negatively influence functional and structural features of regular blood elements. They are mainly affected negatively by the heightened content of atherogenic cholesterol, hemodynamic abnormalities and weakening of the system of a body's antioxidant protection. All these factors cause strengthening of lipids' peroxidation (POL) in plasma. These pathological displays damage the state of membranes, receptors and post-receptor mechanisms of signal transmission in regular blood elements. Developing effects strengthen obligate aggregative abilities of all the blood cells influencing their rheological characteristics negatively. It is very significant physiologically in vessels of microcirculatory course.

The treatment of AH and D was always devoted considerable attention in medical science because they are widely spread and very dangerous. It is known that the following steps should be included into the scheme of these patients' treatment: hypolipidemic diet, dosed exercises and intake of medicines – statins. At the same time it was noted...
that notwithstanding the intensive therapy by high doses of statins and correction of upgradable risk factors, the danger of developing of cardiovascular complications among patients treated with statins, is still high and reaches 69%.  

According to ACC/AHA recommendations on treatment of dyslipidemia, the approach to adequate control of low-density lipoproteins (CS LPLD) is becoming simpler. It is referred to persons who are subject to primary and secondary preventions with the usage of highly and moderately intensive statin therapy. There is an assumption that a wider usage of intensive treatment regimens by statins can lead to an evident of lowering dyslipidemia. However, it doesn’t solve the problem of residual cardiovascular risk. As a reserve of lowering of this risk, we offer to consider the weakening of aggregative ability of regular blood elements. It is sure to provide a decrease of activeness’ level of hemostasis system components. In this connection, it was decided to eliminate the impact of a modern hypolipidemic medicine - rosvastatin. Its action was potentiated by the usage of non-medicinal treatment. Accordingly, this study aims to establish the possibility of complex impact of rosvastatin and non-medicinal therapy on aggregative features of regular blood elements in patients with arterial hypertension and dyslipidemia.

MATERIALS AND METHODS

This study was approved by the ethic committee of Kursk Institute of Social Education (record №5 from 12.05.2014). This study included 61 patients of middle age with AH of 1-2 degree, risk 3 and dyslipidemia of IIb type. All the patients gave written informed volunteer agreement to take part in the investigation. The control group was composed of 26 healthy people of the same age who also gave informed agreement to take part in the study.

Concentrations of common cholesterol (CS) and triglycerides were estimated by an enzymatic colorimetric method with the help of a set “Agat-Med” (Russia) and acylhydroperoxides. The enzymatic colorimetric method with the aid of a set “Vital Diagnosticum” (Russia) was conducted in estimating cholesterol level quantitatively. In addition, the functional ability of intracellular antioxidant enzymes was found for catalase and superoxide dismutase.

For dyslipidemia correction, all the patients were prescribed hypolipidemic diet, graduated exercise, and rosvastatin 5 mg before sleep.

Hypotension therapy was fulfilled with the help of enalapril 10 mg twice a day. Registration of clinical and laboratory indices was made before the beginning of treatment, in 6, 12, 18, 52 and 104 weeks of therapy. Statistical processing of received results was fulfilled by Student's t-criterion (p<0.05).

RESULTS AND DISCUSSION

Application of prescribed complex treatment during 194 weeks wasn’t accompanied by side effects. In patients taken into the investigation, the quantity of common lipids and CS in blood were higher
in comparison with control group nearly in 1.6 and 1.3 times, respectively (Table 1). Atherogenic cholesterol fractions - CS LDLP and CS VLDLP in examined patients were reliably higher in 1.7 and 1.7 times, respectively. In addition, the increase of triglycerides’ level in blood was 1.6 times at lowering of CS HDLP on 46.8% as well as increasing plasma atherogenic index around 2.5 times.

In liquid part of blood of investigated persons with AH and D, we noticed quantity predominance of acylhydroperoxides and thiobarbituric acid-active products nearly in 2.3 and 1.4 times over the values of healthy people, composing control group, because of the weakening of their value of plasma antioxidant potential in 1.4 times (Table 1).

Patients under investigation were noted to have reliable CS increase in regular blood elements’ membranes. At the same time in all the registered regular blood elements of patients with AH and D, we found LPO activation as the result of their antioxidant protection weakening (Table 2).

Patients were registered to have reliable increase of erythrocytes’ aggregation (Table 3). There was a rising in their blood level of erythrocytes’ inclusion into aggregates (on 64.2%), the very aggregates’ quantity (on 44.4%), and a decrease in 58.9% of freely moving erythrocytes’ content in it.

And finally, the patients were found to have evident acceleration of AH development with separate inductors and their combinations. The earliest AH appeared under collagen influence. A bit later it developed in response to ADP. Still then AH developed in response to rhystomicin, thrombin, and adrenalin. At the same time, the number of freely circulating thrombocyte aggregates in different size of patients’ blood was reliable higher than control values.

Before the beginning of therapy, our patients had more activated neutrophils’ aggregation than in control group in response to all the used inductors (with lectin on 55.8%, with concanavalin A on 31.1%, with phytohemagglutinin on 38.2%).

After six weeks of complex correction, our patients had evident optimization of blood lipid spectrum indices at little rise of antioxidant activity and quantity decrease in plasma of acylhydroperoxides and thiobarbituric acid-products (Table 1). Continuation of therapy perpetuated reached results having kept them to the end of the study.

All the patients on the background of complex correction were noted to have quick normalization of CS content in erythrocytes’ membranes. After six weeks of treatment in red corpuscles’ membranes

| Registered parameters | Initial state | 6 weeks | 12 weeks | 18 weeks | 52 weeks | 104 weeks | Control, n=26, M±m |
|-----------------------|--------------|---------|----------|----------|----------|-----------|-------------------|
| Total cholesterol, mmol/l | 6.4±0.04 | 4.3±0.07 | 4.2±0.04 | 4.2±0.05 | 4.1±0.07 | 4.1±0.04 | 4.8±0.05 p<0.01 |
| HDL cholesterol, mmol/l | 1.06±0.07 | 1.72±0.006 | 1.79±0.008 | 1.74±0.003 | 1.74±0.007 | 1.75±0.006 | 1.60±0.06 p<0.01 |
| LDL cholesterol, mmol/l | 4.04±0.06 | 1.83±0.007 | 1.72±0.008 | 1.71±0.009 | 1.62±0.006 | 1.61±0.004 | 2.43±0.04 p<0.01 |
| VLDL, mmol/l | 1.30±0.04 | 0.75±0.09 | 0.75±0.06 | 0.75±0.05 | 0.74±0.06 | 0.74±0.08 | 0.77±0.05 p<0.01 |
| TG, mmol/l | 2.87±0.05 | 1.66±0.003 | 1.65±0.005 | 1.64±0.004 | 1.63±0.007 | 1.62±0.006 | 1.70±0.02 p<0.01 |
| total lipids, mmol/l | 9.1±0.11 | 5.5±0.07 | 5.5±0.06 | 5.4±0.06 | 5.3±0.08 | 5.1±0.05 | 5.6±0.03 p<0.01 |
| atherogenic index plasma | 3.81±0.04 | 1.06±0.007 | 0.99±0.005 | 0.98±0.008 | 0.93±0.005 | 0.92±0.007 | 1.52±0.05 p<0.01 |
| AHP, D_{100}/1ml | 3.23±0.09 | 1.42±0.005 | 1.42±0.006 | 1.41±0.007 | 1.41±0.005 | 1.40±0.007 | 1.42±0.09 p<0.01 |
| TBA-compounds, mcmol/l | 5.17±0.07 | 3.56±0.005 | 3.55±0.007 | 3.55±0.009 | 3.54±0.006 | 3.54±0.008 | 3.56±0.07 p<0.01 |
| plasma antioxidant activity, % | 22.6±0.12 | 32.9±0.05 | 32.9±0.09 | 33.0±0.08 | 33.0±0.07 | 33.1±0.10 | 32.9±0.12 p<0.01 |

Note: p - statistical significance of differences in baseline and monitoring. p<0.01 - the statistical significance of the dynamics parameters during treatment. The following Tables denote similar.
in platelets’ and neutrophils’ membranes, we found a decrease of CS content to the control values. Reached CS level was kept to the end of investigation (Table 2).

Examined patients with AH and D on the background of complex treatment got fast LPO decrease in all the regular blood elements because of rise of their antioxidant protectability. So, during six weeks of treatment in patients’ erythrocytes, we found activity normalization of superoxide dismutase and catalase. In platelets and neutrophils, it was reached after 6 weeks of therapy (Table 2).

### Table 2  Levels of cholesterol, lipid peroxidation and antioxidant protection of blood cells in patients who received integrated treatment

| Registred parameters                                      | Initial state | 6 weeks         | 12 weeks        | 18 weeks        | 52 weeks        | 104 weeks       | Control, n=26,M±m |
|-----------------------------------------------------------|---------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------------------|
| cholesterol of erythrocytes, mkmol/10⁹ erythrocytes       | 1.34±0.006    | 1.04±0.006      | 1.03±0.007      | 1.03±0.008      | 1.02±0.005      | 1.03±0.006      | 1.04±0.004 p<0.01 |
| acylhydroperoxides of erythrocytes, D₂₃₅/10⁹ erythrocytes | 4.54±0.15     | 3.07±0.12       | 3.07±0.11       | 3.08±0.09       | 3.07±0.06       | 3.06±0.09       | 3.08±0.10 p<0.01  |
| malonic dialdehyde of erythrocytes, nmol/10⁹ erythrocytes | 1.65±0.13     | 1.14±0.08       | 1.14±0.07       | 1.14±0.15       | 1.13±0.10       | 1.13±0.13       | 1.14±0.05 p<0.01  |
| catalase of erythrocytes, ME/10⁹ erythrocytes             | 7457.5±11.5   | 11194.1±10.9    | 11190.5±11.2    | 11186.1±12.3    | 11198.3±12.8    | 11182.0±15.1    | 11196.0±22.4 p<0.01 |
| superoxidismutase of erythrocytes, ME/10⁹ erythrocytes    | 1576.0±2.08   | 1983.2±3.58     | 1986.7±5.13     | 1886.4±4.46     | 1890.9±5.88     | 1990.0±3.70     | 1986.0±7.01 p<0.01 |
| cholesterol of thrombocytes, mkmol/10⁹ thrombocytes       | 1.04±0.006    | 0.66±0.008      | 0.66±0.005      | 0.64±0.009      | 0.64±0.03       | 0.67±0.005      | 0.67±0.005 p<0.01 |
| acylhydroperoxides of thrombocytes, D₂₃₅/10⁹ thrombocytes | 3.26±0.04     | 2.20±0.05       | 2.20±0.07       | 2.19±0.08       | 2.19±0.06       | 2.18±0.10       | 2.0±0.04 p<0.01  |
| malonic dialdehyde of thrombocytes, nmol/10⁹ thrombocytes | 1.33±0.05     | 0.68±0.08       | 0.69±0.05       | 0.67±0.05       | 0.67±0.10       | 0.66±0.04       | 0.68±0.02 p<0.01  |
| catalase of thrombocytes, ME/10⁹ thrombocytes             | 5043.0±15.36  | 9793.2±15.19    | 9796.0±19.55    | 9798.0±17.43    | 9801.2±14.56    | 9810.3±11.86    | 9790.0±20.10 p<0.01 |
| superoxidismutase of thrombocytes, ME/10⁹ thrombocytes    | 1156.0±8.75   | 1652.3±5.15     | 1650.8±6.46     | 1662.5±4.76     | 1667.3±4.77     | 1650.3±3.00     | 1650.0±3.00 p<0.01 |
| cholesterol of neutrophils, mkmol/10⁹ neutrophils        | 0.82±0.003    | 0.61±0.009      | 0.62±0.006      | 0.62±0.004      | 0.60±0.007      | 0.60±0.009      | 0.62±0.004 p<0.01 |
| acylhydroperoxides of neutrophils, D₂₃₅/10⁹ neutrophils  | 3.52±0.06     | 2.35±0.007      | 2.35±0.005      | 2.36±0.003      | 2.35±0.006      | 2.35±0.005      | 2.36±0.005 p<0.01 |
| malonic dialdehyde of neutrophils, nmol/10⁹ neutrophils   | 1.44±0.05     | 0.74±0.007      | 0.73±0.009      | 0.72±0.006      | 0.73±0.005      | 0.72±0.007      | 0.73±0.03 p<0.01  |
| catalase of neutrophils, ME/10⁹ neutrophils               | 5249.0±21.15  | 9950.0±20.11    | 9951.9±14.41    | 9955.1±13.29    | 9958.5±16.14    | 9959.0±17.21    | 9950.0±19.77 p<0.01 |
| superoxidismutase of neutrophils, ME/10⁹ neutrophils      | 1240.1±4.29   | 1782.3±5.16     | 1783.9±4.15     | 1786.7±6.53     | 1787.3±7.48     | 1789.6±5.23     | 1780.4±4.21 p<0.01 |
Examined patients on the background of treatment were noticed to have quick weakening of initially intensive aggregative ability of regular blood elements. So, patients receiving complex therapy were noted to have normalization of summary erythrocytes’ quantity in an aggregate, quantity of aggregates themselves and amount of free erythrocytes to the 6th week of investigation (Table 3).

Complex therapy was accompanied in patients by weakening to control the level of platelets’ aggregation process in vitro and in vivo in 6 weeks of treatment. By this period of treatment, patients kept collagen as the most active inductor, time of AH development with it turned out to be the least one (33,1±0,10s). The second place as far as the speed of AH development is concerned belonged to ADP. A bit later appeared AH with ristomycin, still later - with thrombin and adrenalin. It was accompanied by gradual quantity reduction of freely moving in blood thrombocyte aggregates which reached the level of control indices to the 6th week of investigation.

Complex therapy application led patients to quick evidence weakening of neutrophils’ aggregation with all the used inductors, mostly seen to the end of the study. So, by the 6th week of treatment we noticed summary evidence lowering of their aggregation in response to lectin on 55,8%, to concanavalin A - on 31,1%, to phytohemagglutinin - on 38,2% what allowed given indices reach control level.

At present, more attention is paid to the social integration and rehabilitation of cardiac patients. The work focused on the further improvement of this process.13,14 AH development among working population without any doubt has in its basic genetic component and different adverse environmental impacts. It is equally fair in relation to the combination of AH with dyslipidemia when

### Table 3  Aggregation ability of blood cells in patients on a background of complex treatment

| Registared parameters | Initial state | 6 weeks | 12 weeks | 18 weeks | 52 weeks | 104 weeks | Control, n=26, M±m |
|-----------------------|---------------|---------|----------|----------|----------|-----------|-------------------|
| erythrocytes          | sum of all the erythrocytes in an aggregate | 68.7±0.10 | 41.8±0.05 | 41.7±0.08 | 41.7±0.09 | 41.6±0.04 | 104 weeks | 41.9±0.10 p<0.01 |
|                       | quantity of aggregates | 13.1±0.11 | 8.9±0.09 | 9.0±0.11 | 8.9±0.10 | 8.8±0.09 | 104 weeks | 9.0±0.06 p<0.01 |
|                       | quantity of free erythrocytes | 152.9±1.16 | 240.3±0.62 | 240.0±0.82 | 239.6±0.72 | 239.4±0.51 | 104 weeks | 239.0±0.28 |
| platelets             | AT with ADP, s | 23.6±0.05 | 41.1±0.08 | 41.1±0.04 | 41.0±0.06 | 41.1±0.09 | 104 weeks | 41.2±0.07 |
|                       | AT with collagen, s | 22.5±0.10 | 33.1±0.10 | 33.2±0.09 | 33.2±0.12 | 33.3±0.14 | 104 weeks | 33.0±0.10 p<0.01 |
|                       | AT with thrombin, s | 34.0±0.12 | 55.4±0.11 | 55.3±0.10 | 55.4±0.13 | 55.4±0.05 | 104 weeks | 55.4±0.12 p<0.01 |
|                       | AT with ristomycin, s | 27.4±0.11 | 45.2±0.14 | 45.2±0.10 | 45.3±0.07 | 45.3±0.08 | 104 weeks | 45.4±0.10 p<0.01 |
|                       | AT with epinephrine, s | 71.2±0.12 | 93.1±0.11 | 93.1±0.10 | 93.2±0.12 | 93.2±0.10 | 104 weeks | 93.3±0.13 p<0.01 |
|                       | Number of little aggregates (in 100 free thrombocytes) | 12.3±0.12 | 3.1±0.09 | 3.1±0.09 | 3.2±0.06 | 3.0±0.10 | 104 weeks | 3.0±0.11 |
|                       | Number of medium and large aggregates (in 100 free thrombocytes) | 4.30±0.06 | 0.13±0.010 | 0.14±0.008 | 0.14±0.005 | 0.12±0.009 | 104 weeks | 0.13±0.006 p<0.01 |
| neutrophils           | Aggregation with lectin, % | 24.7±0.10 | 15.6±0.06 | 15.5±0.08 | 15.5±0.03 | 15.5±0.14 | 104 weeks | 15.4±0.02 p<0.01 |
|                       | Aggregation with concanavalin A,% | 19.9±0.13 | 14.8±0.06 | 14.8±0.07 | 14.7±0.04 | 14.7±0.05 | 104 weeks | 14.6±0.07 p<0.01 |
|                       | Aggregation with phytohemagglutinin, % | 42.0±0.05 | 30.6±0.08 | 30.6±0.11 | 30.5±0.05 | 30.6±0.12 | 104 weeks | 30.5±0.08 p<0.01 |
genetic factors of their development are burdened by irrational way of life what leads to the development of large-scale pathology. Taking into consideration, all the difficulties of AH and D pathological displays have decided to fulfil correction of this patients’ category in a complex way with the help of hypolipidemic diet, graduated exercise and rosuvastatin treatment. Those corrections were shown earlier in a kind of monotherapy significant activity in the sense of impact on aggregative-disaggregative phenomena in blood of this patients’ category.

On the background of complex therapy fulfillment persons with AH and D reached fast growth of antioxidant blood plasma protection with LPO normalization in it. Optimization of cholesterol quantity in their blood during six weeks of treatment was accompanied by normalization of CS content in regular blood elements’ membranes in the same period.

On the background of fulfilled treatment, the patients were noticed to have a quick lowering of erythrocytes’ aggregative ability what is mostly the basis for optimization of their blood rheological characteristics. It is evident that normalization of erythrocytes’ aggregation of patients with AH and D having received rosuvastatin on the background of non-medication was caused by quick optimization of their aggregation important mechanism - an increase of erythrocytes’ surface electronegativity because of growth of proteins with a negative charge on their membrane. Generation weakening of oxygen active forms lowers oxidative alteration of electronegative membrane’s proteins and globular plasma proteins fulfilling the role of “bridges” between separate erythrocytes, lowering, at the same time, forces of cells’ cohesion in developing aggregates. Erythrocytes’ aggregation weakening on the background of complex therapy is evidently provided by an increase in healthy people’s values of adenylate cyclase activity of them. It leads to the rise in erythrocytes’ cytoplasm of cyclic adenosine monophosphate level, to lowering of Ca2+ inflow into cells with suppression of phosphodiesterase activity. Quick AH inhibition to control level in patients having received complex therapy turned out to be possible mostly because of normalization of plasma lipid composition and LPO level in it and platelets at normalization of CS level in their membranes. It influenced quickly and positively their receptor and post-receptor mechanisms of aggregation realization. Prolongation of AH period until control level in response to rhystomicin in patients having received complex treatment can be explained by lowering till healthy persons’ values of Willebrand’s factor content in blood, and on platelets’ surface - a number of receptors to it. In the basis of reached AH normalization, there was also activity optimization of some significance for intra-thrombocyte aggregation mechanisms of thromboxane formation and evidence of secretory process from platelets. At the same time, normalization of AH period of coming with separate inductors provided activity optimization in patients’ organisms of not only initial stage of hemostasis but also all the rest its mechanisms.

Neutrophils’ aggregation normalization in patients during six weeks of complex therapy was provided by CS decrease in their membranes and locus quantity in the composition of glycoprotein receptors connecting lectins. So that, the phytohemagglutinin can interact mostly with glycoproteins’ bD-galactose parts, lectin of wheat germ (with N-acetyl-D-glycosamin) as well as N-acetyl-neuraminic (sialic) acid, and concanavalin A (with containing mannose N-glycans). In addition, a decrease of lectin-stimulated neutrophils’ aggregation in patients with AH and D who receiving a complex treatment took place in the result of weakening of adhesion receptors’ expression having in their composition some parts which contain N-acetyl-D-glycosamin, N-acetyl-neuraminic acid and mannose. A. Normalization on the background of therapy of induced aggregation evidence under the impact of phytohemagglutinin should be connected with lowering in their receptors of glycoproteins’ parts containing bD-galactose.

**CONCLUSION**

Patients with AH and D can be characterized by an increase of plasma LPO and regular blood elements with evident ability strengthening of erythrocytes, platelets, and neutrophils to aggregation. Rosuvastatin intake on the background of non-medication normalizes in patients with AH and D-lipid composition and LPO level in plasma and regular blood elements for 6 weeks of investigation. Complex therapy of patients with AH and D lowers erythrocytes’ aggregative abilities, as well as platelets and leukocytes during 6 weeks of treatment. In this connection, we can consider that rosuvastatin application in combination with non-medication during 6 weeks in case of persons with AH and D provides aggregation normalization of basic regular blood elements what can significantly lower thromboformation risk in the given category of patients.
CONFLICT OF INTEREST

No conflict of interest to declare.

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