The combination of arterial hypertension and metabolic syndrome causes a whole complex of disorders in the patients’ body, contributing to the risk of developing thrombosis in them. In this regard, it is very important to develop a comprehensive therapy for this patient population, which positively influences the activity of platelets, which is an important factor in the formation of thrombophilia in them. The aim of the work is to establish the intensity of the dynamics of platelet aggregation ability and the state of functional capabilities, the individual mechanisms of their determining in patients with arterial hypertension of the 3rd degree in the metabolic syndrome. 24 patients with arterial hypertension of the 3rd degree, risk 4, including 10 men and 14 women of mature age, were under observation. The control group consisted of 25 clinically healthy people of similar age. The surplus platelet activity observed in the in vitro and in vivo patients is based on an increase in the adhesive and aggregation activity of platelets with a weakening of their ability to disaggregate, largely due to an imbalance in their blood pressure and anti-aggregational compounds. The complex therapy, including amlodipine, valsartan, pioglitazone, hypocaloric diet and dose physical exercise, provided patients with arterial hypertension 3 degrees with metabolic syndrome after 4 months. Stable normalization of initially high platelet activity, significantly reducing their risk of developing thrombosis, despite the non-strict compliance with the non-drug component of treatment after 16 weeks of treatment.

Keywords: Arterial hypertension; Metabolic syndrome; Thrombocytes; Amlodipine; Valsartan; Non-drug treatment

Materials and Methods

The study included 24 patients with AH of 3 degrees, risk 4, incl. 10 men and 14 women of mature age (49.1 ± 1.9 years). All patients had a combination of AH with a diagnosis in strict accordance with the generally accepted criteria of MS, consisting of a violation of glucose tolerance, hyperlipidemia II b type, abdominal obesity (body mass index more than 30 kg/m2, the ratio of waist volume to hip volume more than 0.85 in women and more than 1.0 in men). The control group consisted of 25 clinically healthy people of similar age. A group of patients and a group of healthy people had a normal amount of platelets in their blood. The blood in both groups was taken after 14 hours of starvation. The content of total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) was determined by the enzymatic colorimetry method using the Vital Diagnosticum kit, the total lipids concentration was determined using the Erba Russ kit. Low-density lipoprotein (LDL) cholesterol was calculated according to W. Friedwald, the cholesterol-lowering lipoprotein cholesterol (VLDL) was calculated by the formula: TG/2.2. The lipid composition was evaluated in full accordance with the Russian recommendations on the diagnosis and correction of lipid metabolism disorders [8]. The activity of lipid peroxidation (LPO) of plasma was detected by the content of thiobarbituric acid (TBA)-active products by a set of the firm "Agat-Med" and acyl hydroperoxides (AGP) [9]. In all patients, the antioxidant potential of the liquid part of the blood was determined [10].

All the subjects surveyed in the plasma determined the endothelin-1 content by radioimmunoassay using DRG reagents (USA), as well as the levels of thromboxane A2 thromboxane B2 metabolite and prostacyclin metabolite 6-keto-prostaglandin Flα by enzyme immunoassay using the "Enzo Life science" (USA). The total content of observed metabolites of nitrogen oxide in the blood was determined by the method of [11]. Aggregation of platelets was evaluated on a two-channel laser analyzer aggregation of platelets ALAT2-"BIOLA" (model LA230-2, Russia) using as inducers ADP (0.5 × 10^{-4} M), collagen (1:2 dilution of the basic suspension), ristomycin (0.8 mg/ml).
In order to correct blood pressure (BP) patients were prescribed amlodipine 10 mg once a day and valsartan 160 mg once a day, to optimize carbohydrate metabolism—pioglitazone at a dose of 30 mg once a day. Non-pharmacological therapy included a hypocaloric diet and feasible regular physical training. Assessment of clinical and laboratory indicators was performed at the beginning of treatment, at 2, 4, 12 and 36 months of therapy. The non-compliance with the non-pharmacological component of the ongoing correction was allowed after 4 months therapy.

Statistical processing of the obtained results was carried out using Student's t-test.

**Results and Discussion**

The initial level of arterial pressure in the patients under observation (systolic-186.1 ± 4.3 mm Hg, diastolic-114.8 ± 3.2 mm Hg) corresponded to grade 3 hypertension. After 2 weeks of therapy, the blood pressure level in the observed patients stabilized at the level: systolic-135.0 ± 2.1 mm Hg, diastolic-85.3 ± 1.3 mm Hg, and remained at the achieved level until the end of the observation.

In the blood of patients, increased amounts of OL and OXC prevailed over control values of 1.67 and 1.30 times, respectively (Table 1). At the same time, in the blood of the observed patients with complicated hypertension of grade 3, MS also showed an increase in HDL cholesterol 1.32 times.

As a result of the use of complex therapy in the blood of patients, a gradual decrease in the levels of OL and OXC, reaching the control values after 4 months, was noted (Table 1). This was accompanied in the observed patients by a decrease in plasma concentrations of LDL cholesterol, LLDPE and TG cholesterol and an increase in HDL cholesterol to control figures after 4 months, with their preservation at the achieved level until the end of the observation. Against this background, the stable normalization of LPO plasma activity was noted in the blood of patients at the same time-4 months later. The content of AGP in it was 1.66 ± 0.005 D/1 ml, TBA-active products 3.41 ± 0.002 μmol/l with optimization of the antioxidant potential of the liquid part of the blood (36.3 ± 0.05%).

The imbalance of metabolites of arachidonic acid—thromboxane B2—was found to be increased in the blood of the persons who made up the observation group, by 84.8%, whereas the level of the derivative of its functional antagonist, 6-keto-prostaglandin F1α, was reduced by 17.9% (Table 1). This was accompanied in the patients with high level of endothelin-1 (21.1 ± 0.27 pg/ml) with a decrease in the amount of total metabolites of nitric oxide in their blood plasma reduced by 28.7%.

The complex therapy was accompanied in patients by gradual normalization of the metabolites of arachidonic acid in blood, a decrease in thromboxane B2 by 85.5%, and an increase in 6-keto-prostaglandin F1α by 14.3% (Table 1). This was accompanied by a decrease in the blood of the examined patients to the level of control of endothelin-1 (8.1 ± 0.22 pg/ml) and an increase in the amount of total metabolites of nitric oxide by (21.9%).

### Table 1

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Observed Patients, n = 24, M ± m</th>
<th>Control, n=25, M ± m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial state</td>
<td>2 months of therapy</td>
</tr>
<tr>
<td>Concentration cholesterol, mmol/l</td>
<td>6.25 ± 0.07</td>
<td>5.79 ± 0.06</td>
</tr>
<tr>
<td>Concentration HDL cholesterol, mmol/l</td>
<td>1.14 ± 0.003</td>
<td>1.31 ± 0.001</td>
</tr>
<tr>
<td>Concentration LDL cholesterol, mmol/l</td>
<td>3.92 ± 0.06</td>
<td>3.42 ± 0.05</td>
</tr>
<tr>
<td>Concentration Cholesterol VLDL, mmol/l</td>
<td>1.19 ± 0.002</td>
<td>1.06 ± 0.003</td>
</tr>
<tr>
<td>Concentration triglycerides, mmol/l</td>
<td>2.63 ± 0.02</td>
<td>2.34 ± 0.008</td>
</tr>
<tr>
<td>Level of total lipids, g/l</td>
<td>8.79 ± 0.03</td>
<td>7.53 ± 0.04</td>
</tr>
<tr>
<td>Concentration acylhydroperoxides plasma, D&lt;sub&gt;233&lt;/sub&gt;/1 ml</td>
<td>3.62 ± 0.03</td>
<td>3.24 ± 0.02</td>
</tr>
<tr>
<td>Thiobarbituric acid-products of</td>
<td>5.76 ± 0.002</td>
<td>5.32 ± 0.003</td>
</tr>
</tbody>
</table>
collagen, while the degree of aggregation with this inductor exceeded patients aggregated in response to the addition of ADP. In this case, the control by 25.0% and the aggregation rate by 27.5%. Slightly less normalization of collagen aggregation was noted, manifested by a decrease in the aggregation index by 28.8% with a decrease in the aggregation index of control (Table 2). Most actively, their platelets reacted to ristomycin. At the same time, the degree of aggregation with it in patients was above the same extent as in the control.

As a result of the use of complex therapy in observed patients, platelet aggregation experienced a gradual weakening, maximally achieved (Table 2). Most actively, their platelets reacted to ristomycin. At the same time, the degree of aggregation with it in patients was above the same extent as in the control (Table 2).

At the end, platelet aggregation in patients with AH of grade 3 in MS was enhanced (Table 2). Most actively, their platelets reacted to collagen, while the degree of aggregation with this inductor exceeded the control by 25.0% and the aggregation rate by 27.5%. Slightly less normalization of collagen aggregation was noted, manifested by a decrease in the aggregation index by 28.8% with a decrease in the aggregation index of control (Table 2).

### Table 1: Biochemical characteristics of blood plasma in patients with grade 3 arterial hypertension in metabolic syndrome.

At the end, platelet aggregation in patients with AH of grade 3 in MS was enhanced (Table 2). Most actively, their platelets reacted to collagen, while the degree of aggregation with this inductor exceeded the control by 25.0% and the aggregation rate by 27.5%. Slightly less normalization of collagen aggregation was noted, manifested by a decrease in the aggregation index by 28.8% with a decrease in the aggregation index of control (Table 2). Most actively, their platelets reacted to ristomycin. At the same time, the degree of aggregation with it in patients was above the same extent as in the control (Table 2).

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<tr>
<td>Aggregation of platelets with collagen</td>
<td>10.1 ± 0.25</td>
<td>9.0 ± 0.32</td>
</tr>
<tr>
<td>Degree of aggregation, units</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Aggregation rate, units</td>
<td>8.9 ± 0.32</td>
<td>7.8 ± 0.36</td>
</tr>
<tr>
<td>Aggregation of platelets with ADP</td>
<td>9.3 ± 0.34</td>
<td>8.3 ± 0.30</td>
</tr>
<tr>
<td>Degree of aggregation, units</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>
not only peroxide changes in plasma lipids, but also damage to normal platelet activity in all patients until the end of observation. At the time of taking under observation in blood all patients showed elevated BP present in itself has a negative effect on the vascular wall, thereby contributing to the appearance of sometimes thrombotic phenomena [12]. At the same time, the activity of platelet hemostasis was not fully understood, and needs additional evaluation. Moreover, in this category of patients, the degree of violation of the main mechanisms of the formation of thrombocytopathy, as the basis of thrombophilia, is not fully understood [13].

The observed elevated BP present in itself has a negative effect on the vascular wall, causing damage to the endothelium and exposing subendothelial fibers that are able to contact platelets actively. Furthermore, the complex therapy provided stable maintenance of normal platelet activity in all patients until the end of observation.

At the time of taking under observation in blood all patients detected an increase in the concentration of TG, OX, VLDL cholesterol, LDL cholesterol, which threatened rapid progression in this category of atherosclerosis patients. At the basis of the formation of atherogenic danger, an increase in LPO in the blood, which causes not only peroxide changes in plasma lipids, but also damage to endotheliocytes, played a big role, which facilitated the penetration of lipids into the vessel wall, thereby creating conditions for the subsequent occurrence of thrombosis in them [18]. The complex correction provided stable elimination of dyslipidemia within 4 months. Therapy, which, combined with an increase in antioxidant plasma safety and a decrease in the concentration of primary and secondary LPO products, minimized the risk of progression in observed patients of atherosclerosis.

In previous studies, it was found that hypertension in patients with MS actively violates the functions of the vascular wall and platelets, thereby contributing to the appearance of sometimes thrombotic phenomena [12]. At the same time, the activity of platelet hemostasis in these patients is still not fully understood, and needs additional evaluation. Moreover, in this category of patients, the degree of violation of the main mechanisms of the formation of thrombocytopathy, as the basis of thrombophilia, is not fully understood [13].

The observed elevated BP present in itself has a negative effect on the vascular wall, causing damage to the endothelium and exposing subendothelial fibers that are able to contact platelets actively. The hypercholesterolemia existing in patients, in turn, significantly aggravates this process, accelerating the development of vasopathy [14]. In the emerging conditions in the vascular wall, the synthesis of

Table 2: Functional activity of platelets in patients with grade 3 arterial hypertension in metabolic syndrome.

| aggregation rate, units | Aggregation of platelets with ristomycin degree of aggregation, units | Aggregation rate, units | number of platelets in the aggregates, % | number of small aggregates of 2-3 platelets per 100 free-standing platelets | number of medium and large aggregates, 4 or more platelets per 100 free-standing platelets | erythrocytes-discocytes, % | Disco-echinocytes, % | Spherocytes, % | Sphero-echinocytes, % | Bipolar forms, % | Sum of active forms, % |
|------------------------|-------------------------------------------------|------------------------|------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------|----------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| 8.3 ± 0.29             | 9.4 ± 0.22                                      | 8.5 ± 0.30             | 15.5 ± 0.04                              | 18.2 ± 0.09                                                     | 5.7 ± 0.03                                      | 49.4 ± 0.20                                      |
| 7.2 ± 0.27             | 8.5 ± 0.29                                      | 7.2 ± 0.26             | 12.5 ± 0.07                              | 14.4 ± 0.04                                                     | 2 ± 0.05                                       | 59.5 ± 0.05                                      |
| 5.7 ± 0.23             | 7.3 ± 0.28                                      | 5.4 ± 0.22             | 6.9 ± 0.07                               | 3.1 ± 0.02                                                      | 0.28 ± 0.004                                   | 80.7 ± 0.05                                      |
| 5.6 ± 0.15             | 7.4 ± 0.18                                      | 5.3 ± 0.26             | 0.07                                     | 3.3 ± 0.02                                                      | 0.28 ± 0.002                                   | 80.7 ± 0.05                                      |
| 5.5 ± 0.22             | 7.3 ± 0.23                                      | 5.2 ± 0.19             |                                         | 3.7 ± 0.05                                                      | 0.29 ± 0.003                                   | 79.8 ± 0.05                                      |
| 5.6 ± 0.16             | 7.4 ± 0.15                                      | 5.3 ± 0.22             |                                         | 2.9 ± 0.06                                                      | 0.2 ± 0.06                                     | 77.5 ± 0.70                                      |
| p<0.01                 | p<0.01                                          | p<0.01                 |                                         | p<0.01                                                         | p<0.01                                        | 82.1 ± 0.10                                      |
| p<0.01                 | p<0.01                                          | p<0.01                 |                                         | p<0.01                                                         | p<0.01                                        | 82.1 ± 0.10                                      |
| p<0.01                 | p<0.01                                          | p<0.01                 |                                         | p<0.01                                                         | p<0.01                                        | 81.0 ± 0.10                                      |
| p<0.01                 | p<0.01                                          | p<0.01                 |                                         | p<0.01                                                         | p<0.01                                        | 81.0 ± 0.10                                      |

Conduction of complex therapy provided for the observed patients rapid weakening of BAT, which allowed, after 4 months. To achieve normalization level of discocytes (80.7 ± 0.20%). At the same time, the number of disco-echinocytes in their blood decreased twice, and initially increased number of spherocytes, sphero-echinocytes and bipolar forms of platelets after 4 months. The monitoring also reached the indicators characteristic of control. This provided a decrease in the total number of active platelet forms to the level of the control group (19.3 ± 0.03%), also in the blood of individuals to the observation of the main mechanisms of the formation of atherogenic danger, an increase in LPO in the blood, which causes not only peroxide changes in plasma lipids, but also damage to endotheliocytes, played a big role, which facilitated the penetration of lipids into the vessel wall, thereby creating conditions for the
biologically active substances that is able to limit the adhesion and aggregation of platelets, in which the synthesis of proaggregants is increased [15]. Thus, the intensification of thromboxane formation and the weakening of the production of its functional prostacyclin antagonist, observed in the observed patients, create an imbalance in the metabolites of arachidonic acid, apparently based on the activation of platelet thromboxane synthetase and depression of vascular prostacyclin-synthetic activity. These disorders are exacerbated by the developing increase in production in the wall of the vessels of edothelin-1 and the weakening of the production of NO in it; probably as a result of suppression of endothelial NO synthase by excessive LPO and dyslipidemic changes in plasma [16].

The normalization of blood pressure achieved on the background of treatment quickly eliminates the negative effect of hemodynamic disturbances on the vascular wall peculiar to hypertension, minimizing the alteration of the endothelium and the expression of subendothelial fibers capable of activating platelets [17]. Early relief of hypercholesterolemia also significantly weakened the vasopathy by activating in the vessel wall the synthesis of biologically active substances inhibiting adhesion and aggregation of platelets while physiological weakening of the synthesis of proagregantes in them. This manifested itself in patients after 4 months, recovery against the background of complex therapy to the level of control of the balance of thromboxane and prostacyclin, as judged by the dynamics of the concentration of their metabolites. The rapidly advancing positive changes were combined with the suppression of the production in the wall of the edothelin-1 vessels and the increase in the production of NO in it, probably as a result of the activation of endothelial NO synthase against the background of normalization of LPO and elimination of dyslipidemia.

Developing with AH and MS biochemical changes in blood plasma are inevitably accompanied by an increase in AT, which was noted for all tested inducers. Excessively formed on their membranes, plasma thromboplastin stimulates thrombin formation, leading to the growth of aggregates of the blood platelets and the acceleration of the formation of fibrin fibers on them with the formation of platelet-fibrin clots capable of embolizing small vessels [18,19].

As a result of the therapy, after 4 months not only the optimization of the biochemical plasma disorders present in patients, but also the attenuation of AT, which was noted for all tested inducers. Thromboplastin generation was reduced on thrombocyte membranes of treated patients, which can inhibit thrombin formation, reducing the formation of aggregates of blood plates and suppressing fibrinogenesis, which eliminated the formation of mobile platelet-fibrin clots.

The initially high sensitivity of platelets to the aggregation inducers found in the examined patients was provided through the activation of a number of mechanisms. Thus, on the surface of platelets, a significant increase in the density of glycoproteins Ia-IIa and VI, participating in the activity of platelet thromboxane synthetase and depression of vascular prostacyclin-synthetic activity. These disorders are exacerbated by the developing increase in production in the wall of the vessels of edothelin-1 and the weakening of the production of NO in it; probably as a result of suppression of endothelial NO synthase by excessive LPO and dyslipidemic changes in plasma [16].

The ADP inducer, which belongs to the weak inducers of platelet aggregation, under conditions of lack of formation in the vessels of nitric oxide and prostacyclin also actively, interacts with its own receptors on the membranes of the blood platelets. This causes on them a powerful expression of fibrinogen receptors with activation of phospholipase C2, which provides the cleavage of arachidonic acid from membrane phospholipids [23,24].

The performed therapy was able not only to increase the production of NO and prostacyclin in the vessels, but also to lower the sensitivity of platelets to the inducers of their aggregation. So, on their surface in treated patients after 4 months, observations developed, judging by the weakening of AT in response to collagen, a significant decrease in the density of glycoproteins Ia-IIa and VI, involved in the adhesion of blood platelets. The observed normalization of adhesion of the blood platelets against the background of therapy in the patients was also weakened due to a decrease in the number of receptors to the von Willebrand factor, as indicated by inhibition to the level of control of AT with ristomycin.

The use of complex therapy provided in patients with AH of 3 degrees with MS a decrease in the platelet surface of the sites of fixation of a strong collagen inducer. This was based on a decrease in the activity of phospholipase C, a weakening of the synthesis of diacylglycerol and protein kinase C, followed by pronounced phosphorylation of the proteins of the contractile system. Under these conditions, inositol trisphosphate actively stimulates the entry of Ca^{2+} from the depot of the blood platelets, contributing to the rapid reduction of actomyosin [21,22].

At the same time, against the background of the inadequate synthesis in the vessels of physiological antiplatelet agents in patients with AH of the third degree in MS on the surface of platelets, the number of receptors to collagen increases, this increases their sensitivity to it. This is inevitably accompanied by activation of phospholipase C, stimulation of the synthesis of diacylglycerol and protein kinase C, followed by pronounced phosphorylation of the proteins of the contractile system. Under these conditions, inositol trisphosphate actively stimulates the entry of Ca^{2+} from the depot of the blood platelets, contributing to the rapid reduction of actomyosin [21,22].

Excess blood of patients with active forms of platelets has its basis on the one hand, insufficient formation in vascular walls of nitric oxide and prostacyclin, and, on the other, increasing the activity of platelets themselves. In addition, the high BAT indicates excessive availability of platelet collagen vascular endothelial damage as a result of a high constant presence in the blood of patients with elevated concentrations of dissolved inducers aggregation of a large number of lipid peroxidation and active, leading to chemical endothelial injury [28].
Constantly high blood pressure leads to mechanical microtrauma of the vascular walls, which also inevitably leads to an increase in BAT in the examined contingent of patients. Developing increase in the content of active forms of platelets contributes to the increase of blood-moving aggregates of different sizes, also capable of damaging endotheliocytes, which further reveals subendothelial structures [29]. These processes close the "vicious circle", causing a significant weakening of vascular hemostasis and an increased risk of thrombosis [30]. Also circulating aggregates generalized block vasa vasorum that in the context of existing metabolic disorders and rheological blood of people with hypertension in MS leads to a further weakening of the functions of blood vessels and progression of atherosclerosis.

Complex therapy caused a rapid reduction in the blood of patients in the number of active forms of blood platelets, which was based, on the one hand, on the increase in the formation of nitric oxide and prostacyclin in the vascular walls, and on the other, the weakening of the activity of the platelets themselves. At the same time, inhibition of BAT on the background of the performed treatment speaks about optimization of accessibility of collagen to the vascular wall for blood clots due to minimization of chemical damage to its endothelium by a drop in the amount of dissolved aggregation inducers, lipids and LPO products in the blood of patients. Stable normalization of blood pressure eliminated mechanical microtraction of the vascular walls, which also led to a decrease in BAT in the surveyed patients [31]. The reduction in the active platelet form in these conditions was accompanied by a normalization of the number of aggregates of different sizes moving across the blood, which also played a role in normalizing mechanical effects on endotheliocytes, reducing the contact of the subendothelial structures with blood to the minima. The effects achieved by treatment disrupt the "vicious circle", providing a significant increase in vascular control over platelets, significantly reducing the risk of recurrent thrombosis [32] and improving the quality of life of patients [33,34].

Conclusion

Excessive platelet activity, which is detected in vitro and in vivo in patients with hypertension with MC, is based on an increase in the adhesive and aggregation activity of platelets with a weakening of their ability to disaggregate. This was due to an imbalance in the blood of these patients and anti-aggregation compounds. The most significant causative factors of this imbalance are arterial hypertension, negative changes in the lipid composition of the plasma, and the enhancement of LPO in it. The complex therapy, including amlodipine, valsartan, pioglitazone, hypocaloric diet and dose physical exercise, was provided in patients with AH of grade 3 with MS after 4 months, stable normalization of initially high activity of platelets, significantly reducing their risk of developing thrombosis.

References