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## **DYNAMIC OF INDICES OF LIPID PEROXIDATION AND ANTIOXIDANT PROTECTION IN MUSCULAR TISSUE AND BLOOD SERUM OF RATS WITH ACUTE ISCHEMIA-REPERFUSION**

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### **Abstract**

Acute limb ischemia occurs as a result of sudden decrease in its perfusion, which usually occurs during the obturation of the lumen of large arteries due to acute thrombosis or embolism either impaired of vascular patency caused by trauma or compression (including the application of hemostatic tourniquets). In the case of restoration of blood supply to previously ischemic tissues, there is an ischemic-reperfusion syndrome, in which one of the main pathogenetic links of tissue alteration is the activation of lipid peroxidation.

The content of diene conjugates, triene conjugates, TBA-active products, superoxide dismutase and catalase in homogenate of the muscle tissue and blood serum of 30 white rats under condition of experimental acute ischemia was determined. Acute ischemia was caused by the application of SWAT (Stretch-Wrap-And-Tuck) rubber bundles on the hind limbs of the animals for 2 hours.

It was experimentally found that the maximum increase in the content of diene and triene conjugates in the injured muscle tissue of the animals occurred in the early post-ischemic period on the 2nd hour of reperfusion with a decreasing on the 1st and 7th day and

the subsequent return of indicators in the late postischemic period on the 14th day to the level of control group. The increasing of TBA-active products in the muscle tissue occurred in the first three groups of the rats and peaked in the third group (reperfusion for the 1st day), after which their level decreased in the animals during the late reperfusion period, reaching in the last group on the 14th day of reperfusion indices, close to the values of the control group.

The dynamics of activity of superoxide dismutase and catalase in the muscle homogenate were to a large extent similar (as indicated by the strong positive correlation (+0,99) between them), gradually increasing and reaching the maximum on 7th day of the ischemia-reperfusion syndrome. As a result of the experiment, a decreasing in the antioxidant-prooxidant index in all experimental groups of the rats was also observed in the muscle homogenate, which was the most pronounced on the 1st day of ischemia-reperfusion.

The comparative analysis of the similar parameters of lipid peroxidation and antioxidant protection in the muscle homogenate and blood serum showed a direct correlation in all the studied pairs. The strong and moderate positive correlation between analogous indices of LPO and AOP in muscle homogenate and blood serum in all five studied pairs indicates similar changes of these indicators at the local and systemic levels.

**Keywords: acute ischemia, muscle tissue, ischemia-reperfusion syndrome, lipid peroxidation, antioxidant protection.**

**Introduction.** Acute ischemia arises by a sudden decrease in limb perfusion, causing a potential threat to its viability. Frequent causes of this condition are obturation of the lumen of large arteries due to acute thrombosis or embolism and impaired vascular permeability caused by their injuries or contraction (including the imposition of haemostatic tourniquets) [1, 8]. The incidence of acute limb ischemia is 140 cases per million population per year [2, 3]. In case of restoration of blood supply to previously ischemic tissues arises a multifactorial lesions of tissues, which is called the ischemia-reperfusion syndrome (IRS). IRS is characterized by impairment of cellular metabolism, accumulation of metabolic products in non-physiological concentrations and the development of endogenous intoxication, which are important mechanisms for tissue alteration [4, 5, 6, 7, 8, 9, 10].

The role of lipid peroxidation (LPO) activation in the pathogenesis of IRS is described in a number of publications [11, 12, 13, 14, 15, 16, 17, 18], but the dynamic of LPO at the local level in different periods of ischemia-reperfusion remains insufficiently studied.

Therefore, **the aim** of our work was to analyze the dynamics of changes in lipid peroxidation and antioxidant protection in muscle homogenate and blood serum in acute ischemia caused by the imposition of an arterial tourniquet on the hind limbs of rats.

**Materials and methods.** The content of diene conjugates (DC), triene conjugates (TC) and TBA-active products (TBA-AP) as well as superoxide dismutase (SOD) and catalase activity in homogenate of the muscle tissue and blood serum of 30 white rats under condition of experimental acute ischemia was determined. The acute ischemia was caused by the application of SWAT (Stretch-Wrap-And-Tuck) rubber bundles on the hind limbs of the animals for 2 hours under thiopental sodium anesthesia. The reperfusion syndrome was modeled by restoring blood circulation in previously ischemic limbs after removing the tourniquet.

During the experiment, the animals were divided into 5 study groups of 6 animals each. In the control group there were 5 intact animals. The model of the early post-ischemic period was represented by groups of animals with reperfusion changes at the 1st hour, the 2nd hour and the 1st day after removing the tourniquet, and the model of the late post-ischemic period – at the 7th and 14th days after removing the tourniquet. The euthanasia of animals was conducted by decapitation under thiopental sodium anesthesia.

Blood for the study was obtained from the heart apex of the experimental rats by cardiomy before decapitation. The serum was separated by centrifuging the blood for 15 minutes at 3000 rpm, then cooled. Muscle tissue homogenate was obtained by grinding 0,5 g of ischemic quadriceps femoris muscle in 4,5 ml of saline solution using a «Silent Crasher S Homogenizer» apparatus, followed by centrifugation for 15 minutes at 3000 rpm. The supernatant was collected and used for the study. Determination of the content of DC, TC and TBA-AP as well as SOD and catalase activity in each experimental group was conducted by using generally accepted methods [19, 20, 21, 22].

Antioxidant-prooxidant index (API), which belongs to sensitive indicators of antioxidant protection (AOP) and reflects a balance between prooxidant and antioxidant mechanisms, was calculated by the formula:  $API = \text{catalase activity} / \text{the content of TBA-active products}$  [23].

Statistical processing of the results was performed using the Microsoft Excel software package (Microsoft Office 2007). The following indicators were determined: arithmetic mean (M), standard deviation ( $\sigma$ ) and standard error of the arithmetic mean (m). The statistical significance of the differences between the arithmetic averages and relative values in the normal distribution was assessed by the Student-Fisher criterion (t). By comparing groups of

the same type, correlation analysis was performed taking into account the correlation coefficient (r) using the Pearson squares method.

**Results.** At the first stage of the experiment the dynamics of indicators of LPO and AOP in the muscle homogenate of ischemic limbs of rats was studied. The obtained values of DC, TC, TBA-AP, SOD and catalase are presented in tab. 1.

Table 1. Indicators LPO and AOP in muscle homogenate in different periods of ischemia-reperfusion ( $M \pm m$ ).

	Diene conjugates, conv. units/g	Triene conjugates, conv. units/g	TBA-active products, $\mu\text{mol/kg}$	Superoxide dismutase, conv. units	Catalase, cat/kg
Control Group	0,103±0,016	0,060±0,08	5,57±0,37	68,82±4,53	43,28±1,70
Reperfusion, 1 hour	0,115±0,012	0,078±0,011	6,30±0,26*	70,80±4,90*	43,78±1,85
Reperfusion, 2hours	0,133±0,012*	0,096±0,022	8,03±0,16*/**	75,34±4,40*/***	47,40±1,74*/**
Reperfusion, 1 day	0,124±0,007	0,055±0,015	9,19±0,18*/***	77,44±4,14*/***	49,80±1,43*/**
Reperfusion, 7 days	0,091±0,009*/**	0,041±0,009	8,26±0,19*/**	83,96±3,51*	53,54±1,94*/**
Reperfusion, 14 days	0,108±0,006	0,059±0,020	7,47±0,26*/**	73,52±4,07*/**	46,52±2,08*/***
Notes: * - $P < 0,05$ relative to the control group; ** - $P < 0,05$ relative to the previous group; *** - $P < 0,005$ relative to the previous group					

Studies have shown that the modeling of the IRS was accompanied by an increase of LPO products in the homogenate of ischemic skeletal muscles of experimental animals in the early postischemic period. The maximum statistically significant increase in the level of DC by 29,57% ( $P < 0,05$ ) in comparison with the control group was observed in rats with 2-hour reperfusion. On the 14th day, the indicator of their content was close to the value of the control group (exceeding it only by 5,06% ( $P > 0,05$ )).

The maximum content of TC (60,0% above the control group) was observed in animals with a 2-hour reperfusion ( $P > 0,05$ ). The indicator reached its minimum value on the 7th day of the experiment, being 31,33% lower than the indicator of control group ( $P > 0,05$ ), and on the 14th day of the IRS there was no statistically significant difference in the TC content compared to the control group ( $P > 0,05$ ).

In all experimental groups of rats of the early reperfusion period in the muscle homogenate statistically significant increase in the content of TBA-AP was observed. This indicator reached its maximum in the third group of rats (reperfusion for 1 day) and was higher than the index of control group by 64,86%, which turned out to be statistically significant ( $P < 0,005$ ). On the 14th day, this indicator reached its minimum value, being only 34,1% higher than the index of control group ( $P < 0,05$ ).

A statistically significant increase in the SOD activity relative to the control group in all three groups of rats of the early reperfusion period was recorded, and this indicator reached its maximum in animals with a reperfusion on the 7th day, being by 22,0% higher than the indicator of control group ( $P < 0,05$ ). On the 14th day of the experiment, the SOD activity decreased and only by 6,83% exceeded the value of the indicator of the control group ( $P < 0,05$ ).

An increase of catalase activity in the muscle tissue homogenate of rats was detected during the experiment. On the 1st day of reperfusion, the indicator was 15,06% higher than the corresponding indicator of the control group ( $P < 0,005$ ), and on the 7th day of reperfusion reached a maximum and was 23,71% higher than the corresponding indicator of the control group ( $P < 0,005$ ). On the 14th day of the experiment, the activity of the indicated enzyme decreased and only 7,49% exceeded the indicator of the control group ( $P < 0,05$ ).

The value of the API index in all experimental groups of animals was statistically significantly lower in comparison with control group (fig. 1). The index gradually decreased in the first two groups of rats and reached the minimum value (5,42 conv. units) in animals with reperfusion for the 1st day, which turned out to be 31,61% lower of the corresponding indicator of the control group ( $P < 0,05$ ).

The correlation analysis of indicators of LPO and AOP in the homogenate of muscle tissue revealed a strong positive correlation between DC and TC (+0,79), between TBA-AP and catalase (+0,75) and between SOD and catalase (+0,99), as well as the moderate positive correlation between TBA-AP and SOD (+0,66). Between DC and TBA-AP (-0,39), DC and SOD (-0,54), DC and catalase (-0,49), TC and SOD (-0,66) and TC and catalase (-0,69) there was a moderate negative correlation, and between TC and TBA-AP the negative correlation was weak (-0,19).

Simultaneously with the determination of the content of the LPO and AOP products in the homogenate of muscle tissue, they were also determined in the blood serum of rats (tab. 2). During the 1st hour of the IRS, there was a statistically significant increase in the content of DC by 47,17% ( $P < 0,05$ ), and the maximum value DC was reached in the third group

(reperfusion for the 1st day) and was 66,04% higher than the index of control group ( $P>0,05$ ). On the 14th day, the indicator was only 16,04% higher than the same indicator of the control group ( $P>0,05$ ).

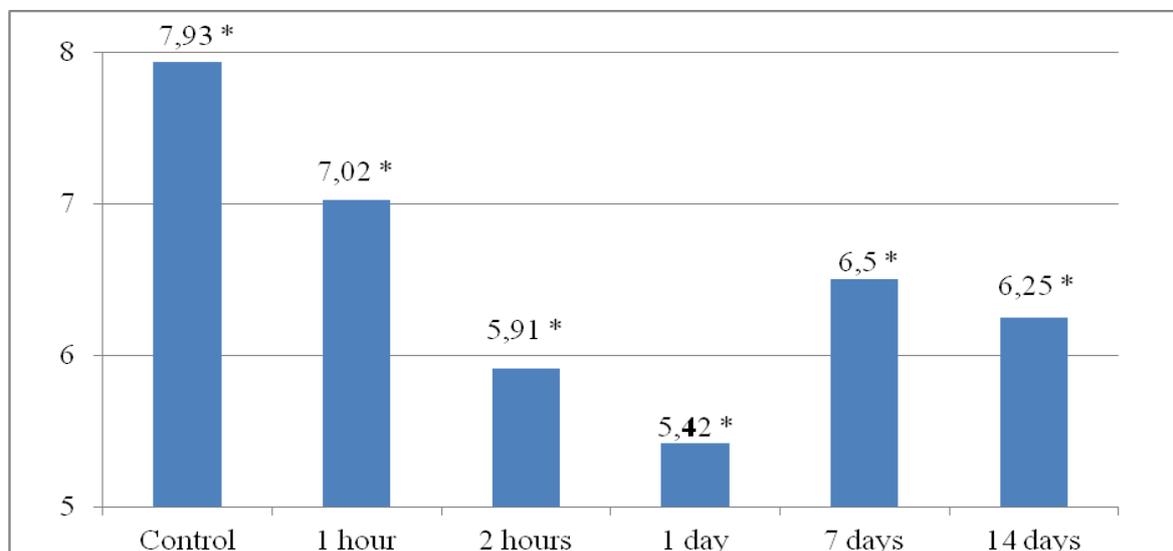


Figure 1. Dynamics of the antioxidant-prooxidant index (in conventional units) in the muscle homogenate of the ischemic limb of rats during different periods of ischemia-reperfusion. (Notes: \* - ( $P<0,05$ )).

Table 2. Indicators LPO and AOP in the blood serum of rats in different periods of ischemia-reperfusion ( $M \pm m$ )

	Diene conjugates, conv. units / g	Triene conjugates, conv. units / g	TBA-active products, $\mu\text{mol} / \text{kg}$	Superoxide dismutase, conv. units	Catalase, cat / kg
Control group	$0,42 \pm 0,11$	$0,28 \pm 0,04$	$2,98 \pm 0,27$	$54,84 \pm 3,92$	$32,44 \pm 1,83$
Reperfusion, 1 hour	$0,62 \pm 0,13^*$	$1,33 \pm 0,37$	$3,21 \pm 0,23^*$	$54,52 \pm 4,61$	$32,72 \pm 1,86$
Reperfusion, 2 hours	$0,53 \pm 0,06$	$2,54 \pm 0,23^*$	$4,34 \pm 0,40^*/$ **	$64,72 \pm 4,54^*$	$51,60 \pm 1,08^*/$ ***
Reperfusion, 1 day	$0,70 \pm 0,11$	$1,36 \pm 0,12^*/$ **	$4,93 \pm 0,22^*$	$72,08 \pm 1,70^*$	$50,64 \pm 1,68^*$
Reperfusion, 7 days	$0,53 \pm 0,16$	$0,35 \pm 0,10$ ***	$3,93 \pm 0,30^*/$ **	$59,96 \pm 2,92^*/$ **	$40,22 \pm 1,04^*/$ **
Reperfusion, 14 days	$0,49 \pm 0,10$	$0,51 \pm 0,15$	$3,41 \pm 0,24$	$54,92 \pm 2,79^{**}$	$33,46 \pm 2,05$

Notes: \* -  $P<0,05$  relative to the control group; \*\* -  $P<0,05$  relative to the previous group; \*\*\* -  $P<0,005$  relative to the previous group

A statistically significant increase in the content of TC in the blood serum of the 1st group of rats 3,82 times ( $P < 0,05$ ) and of the 2nd group of animals 8,22 times ( $P < 0,0005$ ) in comparison with the control group was observed, with a subsequent decrease in the content in the last three groups of animals.

A statistically significant increase of concentration the TBA-AP in the blood serum of rats in almost all experimental groups was observed. On the 1st day, this indicator reached its maximum value and exceeded the indicator of the control group by 65,79% ( $P < 0,005$ ). The TBA-AP indicator reached the minimum value on the 14th day of the IRS (14,52% higher than the same indicator of control group ( $P > 0,05$ )).

When analyzing the content in the serum of AOP enzymes, an increase in SOD activity was noted in the early postischemic period. The maximum level of SOD activity was reached in the third group (reperfusion for 1 day) and was 31,44% higher than the level of control group ( $P < 0,05$ ).

The maximum increase in catalase activity by 59,06% ( $P < 0,0005$ ) was observed in the second group of rats (reperfusion for 2 hours). In animals with reperfusion 1 day the indicator remained almost at the same level (56,10% higher than the control group ( $P < 0,005$ )). On the 14th day, the index activity of catalase decreased to the level of indicator of the control group.

Correlation analysis between indicators of LPO and AOP in the blood serum of the studied animals showed a positive correlation between all the studied parameters. Between TC and catalase (+0,94), TBA-AP and SOD (+0,99), TBA-AP and catalase (+0,94) and SOD and catalase (+0,92) this correlation was strong, between DC and TBA-AP (+0,5), DC and SOD (+0,6), DC and catalase (+0,34), TC and TBA-AP (+0,4) and TC and SOD (+0,43) it was moderate, and between DC and TC (+0,21) the correlation was weak.

In each experimental group of animals, the coefficient of correlation between similar indicators of LPO and AOP in the homogenate of muscle tissue and blood serum was determined. There was a strong positive correlation in the study of the content of the TC (+0,88) and TBA-AP (+0,92), and a moderate positive correlation in the study of the indicators of DC (+0,36), SOD (+0,37) and catalase (+0,39).

**Conclusions.** In the early post-ischemic period, the increase in the content of LPO products (DC, TC and TBA-AP) in the homogenate of damaged muscle tissue occurred starting from the 1st hour of reperfusion. The maximum values of DC and TBA-AP reached at the 2nd hour, and TC on the 1st day of reperfusion. On the 14th day, their content in the muscle homogenate was close to the level of control group.

In the muscle homogenate, a moderate (not exceeding 25% compared to the control group) increase in the activity of AOP enzymes (SOD and catalase) was observed with a maximum on the 7th day of reperfusion, after which on the 14th day the indices decreased to the level of the control group ( $P > 0,05$ ). Thus, an increase in the activity of SOD and catalase by IRS indicates the moderate activation of compensatory mechanisms of AOP in ischemic muscle tissue. The dynamics of changes in the indices of SOD and catalase was synchronous, as evidenced by the strong positive correlation between them (+0,99).

A statistically significant decrease of the API index in the early reperfusion period in the muscle homogenate was observed, which reached a minimum value on the 1st day of reperfusion (31,61% lower than the control group ( $P < 0,05$ )). This indicates an increase in the muscular tissue during this period of imbalance between LPO and AOP in favor of peroxidation.

An increase of the API in the late reperfusion period indicates a gradual restoration of the balance in the system of prooxidants and antioxidants, which is not fully completed on the 14th day of the IRS (the API indicator did not reach the level of the control group). The opposite tendencies in the dynamics of changes in the content of pro- and antioxidants is confirmed by the moderate negative correlation between DC and SOD (-0,54), DC and catalase (-0,49), TC and SOD (-0,66) and TC and catalase (-0,69).

Dynamics of changes in indicators of lipid peroxidation at the systemic level (in blood serum) largely reflected their dynamics at the local level (in muscle homogenate). The maximum increase in TC content at the 2nd hour of reperfusion by 8,2 times and the increase in the 1st day of reperfusion the content of DC and TBA-AP (by 65,79% and 66,04%, respectively) in comparison with the control group confirms the development in experimental animals of IRS with LPO activation.

The dynamics of the decline in LPO at the 7th and 14th days in the blood serum of rats was synchronous with the dynamics of analogous indicators in muscle tissue, and this indicates the restoration of disorders in the soft tissues of the limbs in the late reperfusion period. The positive correlation between all three studied indicators of the LPO indicates a similar trend in the dynamics of changes of these indicators.

By the study of AOP in blood serum, there was an increase in the activity (up to 60%) of SOD and catalase in the early reperfusion period at the 2nd hour and 1st day, with a subsequent decrease in the activity of these enzymes in the late reperfusion period on the 7th day, and returning to the level of control values on the 14th day. The detected direct strong

correlation between the indices of SOD and catalase (+0,92) in the blood serum indicates their synchronous dynamics.

The peak of SOD and catalase activity in the muscle homogenate was on the 7th day, while in the blood serum the maximum activity of these enzymes was observed during the 2nd hour (catalase) and on the 1st day (SOD) of reperfusion. Such dynamics indicates a greater severity of the lesion and a slower tissue restoration at the local level in case of IRS compared with the systemic level. The level of the API in the muscle homogenate in the late postischemic period remained above the values of the control group, which indicates that on the 14th day of reperfusion the restoration of functional activity of the affected muscle tissue have not yet fully completed.

The strong and moderate positive correlation between analogous indices of LPO and AOP in muscle homogenate and blood serum in all five studied pairs indicates similar changes of these indicators at the local and systemic levels.

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