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AGE PECULIARITIES OF 8-ISOPROSTANE SERUM DYNAMICS IN EXPERIMENTAL CRANIO-SKELETAL TRAUMA

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The main peculiarity of modern traumatism is the increasing frequency of severe combined and multiple trauma. Oxidative stress plays a leading role in the pathogenesis of secondary damage in cases of combined trauma. In experiments on rats of different age groups, the effect of combined skeletal and traumatic brain injury on the serum content of 8-isoprostane was studied on 1, 3, 7, 14, 21 and 28 days of post-traumatic period. It was found that modeling of cranio-skeletal trauma among rats of different age groups compared to control group is accompanied by a significant increase in the content of 8-isoprostane in the blood serum. Among immature rats, the index reaches a maximum in 7 days, significantly increases in other experimental groups and normalizes by the 28th day. In old rats, the greatest increase in the content of 8-isoprostane in the blood serum occurs after 3–21 days of the experiment; it is characterized by the lowest amplitude of growth with a further decrease by the 28th day, which does not reach the control level. In terms of the dynamics of 8-isoprostane content in the blood serum the group of mature rats occupies an intermediate position, which corresponds to the antioxidant and restorative capacity of rats of this age group.

Key words: traumatic brain injury, femur fracture, age, oxidative stress, 8-isoprostane.

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ВІКОВІ ОСОБЛИВОСТІ ДИНАМІКИ 8-ІЗОПРОСТАНУ СИРОВАТКИ КРОВІ В УМОВАХ ЕКСПЕРИМЕНТАЛЬНОЇ КРАНІОСКЕЛЕТНОЇ ТРАВМИ

Характерною рисою сучасного травматизму є зростання частоти тяжкої поєднаної та множинної травми. В патогенезі вторинного ураження за умов поєднаної травми провідну роль відіграє оксидативний стрес. В експериментах на щурах різних вікових груп досліджували вплив поєднаної скелетної та черепно-мозкової травми на вміст у сироватці крові 8-ізопростану через 1, 3, 7, 14, 21 та 28 діб посттравматичного періоду. Встановлено, що моделювання краніоскелетної травми у щурів різних вікових груп порівняно з контролем супроводжується суттєвим зростанням вмісту 8-ізопростану в сироватці крові. У статевонезрілих щурів показник досягає максимуму через 7 діб, суттєво перевищує інші дослідні групи й до 28 доби нормалізується. У старих щурів найбільше зростання вмісту 8-ізопростану в сироватці крові настає через 3–21 доби експерименту, характеризується найменшою амплітудою зростання з подальшим зниженням до 28 доби, яке не досягає рівня контролю. Група статевозрілих щурів за динамікою вмісту 8-ізопростану в сироватці крові займає проміжне положення, що відповідає антиоксидантній і відновній спроможності щурів цієї вікової групи.

Ключові слова: черепно-мозкова травма, перелом стегнової кістки, вік, оксидативний стрес, 8-ізопростан.

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The main feature of modern traumatism is the increasing frequency of severe combined and multiple trauma [3]. Its main causes are falls, car accidents, wars, and sports [11]. In the structure of combined trauma, the greatest threat is traumatic brain injury (TBI), which is a proven predictor of mortality in combined trauma among victims of all age groups [1]. The incidence of TBI worldwide is estimated at 939 cases per 100,000, which imposes a significant economic burden on society with annual global costs reaching $400 billion [9].

In the pathogenesis of TBI, there is a phase of primary and secondary damage. Primary damage occurs under the influence of external physical force on the brain, including rupture, contusion, intracranial hemorrhage, and diffuse axonal damage [4]. In the experiment on rats, moderate TBI from the 1st day of the posttraumatic period is accompanied by severe neurological deficits, motor and muscle disorders, which are manifested by muscle weakness, inability to take and hold a natural position with a maximum expression after 14 days of the posttraumatic period [15].

Secondary damage is a delayed reaction that causes long-term neuropathological changes. Depending on the severity of the injury, metabolic and neuroinflammatory disorders occur in the brain, causing axonal damage, neurovascular and final neurodegenerative changes [5].

Oxidative stress (OS) plays a key role in the pathogenesis of secondary brain damage. OS is the result of an imbalance between metabolic processes that lead to the production of active oxygen species

(AOS) and processes responsible for their utilization with the participation of the enzymatic and non-enzymatic antioxidant system [5]. Considering that in normal conditions, the brain uses approximately 20 % of the total amount of oxygen in the body; an increase in its intake, which occurs in the context of TBI, contributes to the increased formation of AOS. Brain tissue is particularly susceptible to oxidative damage due to its high oxidative metabolic activity, relatively low antioxidant capacity, and slow repair mechanisms [2].

A number of studies have shown that TBI in peacetime and under combat conditions is often combined with skeletal bone trauma and is characterized by a particularly severe course and high mortality due to the development of a mutual aggravation syndrome [6]. According to data [7], cranio-skeletal trauma (CST) is accompanied by greater prooxidant disorders than cranio-cerebral and skeletal trauma in particular. Under these conditions, increased lipid peroxidation (LPO) occurs not only in the brain, but has a systemic nature, causing increased lipid peroxidation in internal organs and is considered to be one of the prerequisites for the development of multiorgan dysfunction.

The "golden" standard for assessing the activity of oxidative stress is the determination of 8-isoprostane, which appears in tissues and blood plasma due to non-enzymatic oxidation of cell membrane phospholipids [8]. 8-isoprostane is an isomer of prostaglandin F2 which allows to assess the level of free radical formation with sufficient accuracy, reliability and reproducibility of the study results. However, the age-related dynamics of 8-isoprostane in the blood serum after CST has not been studied.

The purpose of the study was to determine the age-related features of serum 8-isoprostane dynamics under conditions of experimental cranio-skeletal trauma.

Materials and methods. In the experiments, 147 white male rats of different age groups of the Wistar line were used, selected by a random method. The rats were kept on a standard vivarium diet and divided into three experimental groups (42 rats each). The first experimental group consisted of immature rats aged 100–120 days and weighing 90–110 g; the second experimental group consisted of mature rats aged 6–8 months and weighing 180–200 g; the third experimental group consisted of old rats aged 19–23 months and weighing 300–320 g.

All the experiments on causing injuries were performed under thiopental sodium anesthesia (40 mg/kg). Among immature (young) rats, a dosed mechanical damage was applied sequentially to one of the thighs with a solid object with a wedge-shaped nozzle and the energy of 0.320 J; a closed fracture of one femur was achieved; a dosed damage to the skull with the energy of 0.226 J was applied with an object with a blunt end at a point 3 mm anterior to the interauricular line [10].

Among mature (adult) rats, hip fracture was modeled by applying a dosed mechanical damage to the hip with a wedge-shaped impactor with the energy of 0.637 J, which caused a closed fracture of the femur. TBI was induced by a dosed damage to the skull at a point 5 cm anterior to the interauricular line with the energy of 0.375 J [10].

Among old rats, a hip fracture was achieved by applying a dosed damage to the hip with the energy of 0.796 J, and TBI achieved by a dosed damage to the skull with a blunt object with the energy of 0.549 J at a point 6 mm anterior to the interauricular line [10].

The hit energy caused moderate traumatic brain injury among animals of different age groups. In the experiments, no animals with penetrating skull injuries or open hip fractures were used. The control rats (7 rats of each age group, a total of 21) were only injected with thiopental sodium anesthesia.

Animals were taken out from the experiments under thiopental sodium anesthesia after 1, 3, 7, 14, 21, and 28 days by total bleeding from the heart. The concentration of 8-isoprostane was determined in the blood serum by an enzyme-linked immunosorbent assay using ELISA Kit #516351 (Cayman Chemical, USA). The enzyme-linked immunosorbent assay analyzer RT-2100C (Ratyo, China) was used. The result was expressed in pg/ml.

The experiments were performed in accordance with the "General Ethical Principles for Animal Experiments" adopted by the First National Congress on Bioethics (Kyiv, 2001) and harmonized with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), as well as the conclusion of the Bioethics Commission of the I. Horbachevsky Ternopil National Medical University, Ministry of Health of Ukraine No. 72 from 06.01.2023.

Data processing. The obtained digital material was processed in the STATISTICA software package (StatSoft Inc., USA), disk serial number BXXR303F737429FA-8. The median (Me) and the lower and upper quartiles (LQ, UQ) were determined. For an independent comparison of the degree of indicator deviation among animals of different age groups, the ratio of individual values of serum 8-isoprostane due

to the value of the control group was calculated [10]. The significance of differences was assessed by the nonparametric Mann-Whitney test.

Results of the study and their discussion. Research has shown that in control rats group of different ages, the serum content of 8-isoprostane was significantly higher in the group of immature rats compared to the groups of mature and old rats (respectively in 1.24 times (4.42/3.57) p_{1-2}=0.007 and 1.44 times (4.42/3.08) p_{1-3}=0.002) (Table 1).

Table 1

Serum 8-isoprostane content (pg/ml) under the influence of cranioskeletal trauma in rats of different ages, Me (LQ;UQ) – median (lower and upper quartiles)

Group	Control	Term after injury					
		Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
Experimental group 1 Immature	4.42 (4.32; 4.98)	6.30 (5.59; 7.00) p=0.002	9.30 (8.04; 9.62) p=0.002 p_1=0.002	12.51 (10.93; 13.56) p=0.002 p_1=0.002 p_3=0.005	10.50 (9.18; 11.46) p=0.002 p_1=0.002 p_3=0.074 p_7=0.055	5.25 (4.54; 5.86) p=0.041 p_1=0.041 p_3=0.002 p_7=0.002 p_{14}=0.002	4.71 (4.28; 5.71) p=0.898 p_1=0.011 p_3=0.002 p_7=0.002 p_{14}=0.002 p_{21}=0.160
Experimental group 2 Mature	3.57 (3.19; 4.12)	5.98 (4.74; 6.11) p=0.002	7.44 (6.61; 8.28) p=0.002 p_1=0.003	8.78 (7.53; 9.00) p=0.002 p_1=0.002 p_3=0.041	8.75 (7.97; 9.74) p=0.002 p_1=0.002 p_3=0.015 p_7=0.523	5.36 (4.74; 6.29) p=0.030 p_1=0.898 p_3=0.005 p_7=0.002 p_{14}=0.002	5.17 (4.56; 5.20) p=0.005 p_1=0.443 p_3=0.003 p_7=0.002 p_{14}=0.002 p_{21}=0,702
Experimental group 3 Old	3.08 (2.74; 3.42)	5.36 (4.44; 5.91) p=0.002	6.10 (5.15; 6.83) p=0.002 p_1=0.125	6.39 (5.46; 6.91) p=0.002 p_1=0.047 p_3=0.443	6.50 (6.14; 8.11) p=0.002 p_1=0.009 p_3=0.160 p_7=0.250	5.92 (5.27; 6.45) p=0.002 p_1=0.160 p_3=0.702 p_7=0.443 p_{14}=0.055	4.56 (3.80; 5.27) p=0.002 p_1=0.073 p_3=0.011 p_7=0.002 p_{14}=0.002 p_{21}=0.009
p_{1-2}	0.007	0.159	0.015	0.003	0.041	0.609	0.443
p_{1-3}	0.002	0.041	0.002	0.002	0.002	0.125	0.370
p_{2-3}	0.025	0.250	0.030	0.005	0.015	0.371	0.248

Notes. Here and in Table 2: p – significance of differences relative to the control group; p_1 – relative to day 1 of the experiment; p_2 – relative to day 3 of the experiment; p_7 – relative to day 7 of the experiment; p_{14} – relative to day 14 of the experiment; p_{21} – relative to day 21 of the experiment; p_{1-2} – significance of differences between experimental groups 1 and 2; p_{1-3} – significance of differences between experimental groups 1 and 3; p_{2-3} – significance of differences between experimental groups 2 and 3.

At the same time, in the group of mature rats, the index was 1.16 times (3.57/3.08) higher than in the group of old rats, which was statistically significant (p_{2-3}=0.025).

After modeling of CST among immature rats, the content of 8-isoprostane increased in comparison with the control after 1 day of the experiment (1.42 times (6.30/4.42), p=0.002) and reached a maximum after 7 days. During this period, the index was 2.83 times (12.51/4.42) higher than in the control (p=0.002) and statistically significantly higher than the results of the 1-st and 3-rd days of the experiment (p_1=0.002; p_3=0.005).

After 14 days of experiment, the index continued to remain at the level of 7th day (p_7=0.055) and decreased further. After 21 days, the indicator was statistically significantly lower compared to the results of all previous observation periods – 0.83 (5.25/6.30), 0.56 (5.25/9.30), 0.42 (5.25/12.51) and 0.50 (5.25/10.50) times, respectively (p_1=0.041; p_3=0.002; p_7=0.002; p_{14}=0.002). During this period, the index continued to exceed the result of the control group by 1.19 times (5.25/4.42), p=0.041.

After 28 days of the experiment, the content of 8-isoprostane in the blood serum continued to decrease and reached the level of the control group (p=0.898). At this time, the index became statistically significantly lower compared to results of 1, 3, 7 and 14 days of the experiment – 0.75 (4.71/6.30), 0.51 (4.71/9.30), 0.38 (4.71/12.51) and 0.45 times, respectively (p_1=0.011; p_3=0.002; p_7=0.002; p_{14}=0.002), but did not differ statistically significantly from the result of the 21st day of the experiment (p_{21}=0.160).

In the group of mature rats after application of CST, the content of 8-isoprostane in the blood serum increased compared to the control and at all times of the experiment statistically significantly exceeded the level of the control group ($p<0.05$). The index reached a maximum after 7 days of the experiment, 2.46 times (8.78/3.57) higher than the control level ($p=0.002$), 1.47 times (8.78/5.98) – the result of the 1st day of the experiment ($p_1=0.002$) and 1.18 times (8.78/7.44) – the result of the 3rd day of the experiment ($p_3=0.041$). The index remained at the same level after 14 days ($p_7=0.523$) and decreased further.

After 21 days, the index reached the level of the 1st day of the experiment ($p_1=0.443$) and compared with the results of the 3-rd, 7-th and 14-th days of the experiment became statistically significantly lower – 0.72 (5.36/7.44), 0.61 (5.36/8.78) and 0.61 (5.36/8.75) times, respectively ($p_3=0.005$; $p_7=0.002$; $p_{14}=0.002$). After 28 days, the index continued to decrease, but the differences between the results of the 1-st and 21-th days were not statistically significant ($p_1=0.443$; $p_{21}=0.702$). Compared to the results of the 3-rd, 7 and 14 days of observation, the value of the studied indicator became significantly lower – 0.69 (5.17/7.44), 0.59 (5.17/8.78) and 0.59 (5.174/8.75) times, respectively ($p_3=0.003$; $p_7=0.002$; $p_{14}=0.002$).

In the group of old rats, the modeling of CST compared with the control was also accompanied by the increase in the content of 8-isoprostane in the blood serum at all times of the posttraumatic period ($p<0.05$). In the dynamics, the index gradually increased and reached a maximum after 7 days of the experiment. At this time, the index significantly exceeded the result of the 1st day of the experiment (1.19 times (6.39/5.36), $p_1=0.047$). Subsequently, after 14 and 21 days of the experiment, the content of 8-isoprostane in the blood serum continued to remain at the level of 7th day ($p_7=0.250$, $p_{14}=0.055$), and only after 28 days it decreased. During this period, the index reached the level of the 1st day of the experiment ($p_1=0.073$) and was statistically significantly lower compared to the results of 3, 7, 14 and 21 days – 0.74 (4.56/6.10), 0.71 (4.56/6.39), 0.70 (4.56/6.50), respectively ($p_3=0.011$; $p_7=0.002$; $p_{14}=0.002$; $p_{21}=0.009$).

The comparison of the experimental groups of different age in the dynamics of CST by the content of 8-isoprostane in the blood serum showed that after 1 day of the posttraumatic period, the index was statistically significantly higher in experimental group 1 compared to experimental group 3 - 1.18 times (6.30/5.36), $_{p1-3}$= 0.041. In experimental group 2, the value of the index did not differ significantly compared to experimental groups 1 and 3 (p_{1-2} =0.159; p_{2-3} =0.250). After the 3rd, 7th and 14th days of the post-traumatic period, we identified the tendency that with increasing age, the serum 8-isoprostane content became significantly lower. Under these conditions, statistically significant differences were noted between the experimental groups of different ages ($p_{1-2}<0.05$, $p_{1-3}<0.05$, $p_{2-3}<0.05$). At the same time, after 21 and 28 days of the posttraumatic period, the differences in the content of 8-isoprostane in the blood serum between the experimental groups were not statistically significant ($p_{1-2}>0.05$, $p_{1-3}>0.05$, $p_{2-3}>0.05$).

The analysis of the mean ratio of individual values of serum 8-isoprostane to the average value of the control group under the influence of CST showed that in experimental groups 1, 2 and 3 the value of this indicator after 1, 3 and 14 days of the posttraumatic period was practically the same ($p_{1-2}>0.05$; $p_{1-3}1>0.05$; $p_{2-3}>0.05$) (Table 2).

Table 2

Dynamics under the influence of cranioskeletal trauma among rats of different ages, Me (LQ; UQ) – median (lower and upper quartiles)

Group	Term after injury					
	Day 1	Day 3	Day 7	Day 14	Day 21	Day 28
Experimental group 1 Immature	1.43 (1.26; 1.58)	2.10 (1.82; 2.18)	2.83 (2.47; 3.07)	2.38 (2.08; 2.59)	1.19 (1.03; 1.33)	1.07 (0.97; 1.29)
Experimental group 2 Mature	1.68 (1.33; 1.71)	2.08 (1.85; 2.32)	2.46 (2.11; 2.52)	2.45 (2.23; 2.73)	1.50 (1.33; 1.76)	1.45 (1.28; 1.46)
Experimental group 3 Old	1.74 (1.44; 1.92)	1.98 (1.67; 2.22)	2.07 (1.77; 2.24)	2.11 (1.99; 2.63)	1.92 (1.71; 2.09)	1.48 (1.23; 1.71)
p_{1-2}	0.125	1.000	0.041	0.523	0.055	0.011
p_{1-3}	0.055	0.7988	0.007	0.523	0.002	0.015
p_{2-3}	0.201	0.523	0.074	0.160	0.021	0.701

After 7 days, the index in studied group 1 was significantly higher than in studied groups 2 and 3 – 1.15 (2.83/2.46) and 1.37 (2.83/2.07) times, respectively ($p_{1-2}=0.041$, $p_{1-3}<0.007$). At the same time, the value of the index in experimental groups 2 and 3 was almost the same ($p=0.074$).

However, starting from the 21-th day, the value of the average ratio of individual values of serum 8-isoprostane to the average value of the control group under the influence of CST began to increase with increasing age. During this period, in study group 3, the index became significantly higher than in study groups 2 and 3 – by 1.61 (1.92/1.19) and 1.28 (1.92/1.50) times, respectively ($p_{1-3}=0.002$; $p_{2-3}=0.021$). The differences between experimental groups 1 and 2 were not statistically significant ($p_{1-2}=0.055$).

After 28 days, the index was significantly higher in experimental groups 2 and 3 compared to experimental group 1 – by 1.36 (1.45/1.07) and 1.38 (1.48/1.07) times, respectively (p_{1-2}=0.011; p_{1-3}=0.015). The differences between experimental groups 2 and 3 were not statistically significant (p_{1-2}=0.055).

The obtained results indicate that modeling of CST among rats of different age groups compared to control is accompanied by an increase in lipid peroxidation processes in the body, which was detected on the basis of an increase in the concentration of 8-isoprostane in the blood serum. The general pattern of increased lipid peroxidation, regardless of age, is its biphasic nature with a period of increase (up to the middle of the experiment) and subsequent decrease – up to the 28-th day. A similar tendency of increased lipid peroxidation in internal organs in mature rats was noted by other authors, confirming the systemic nature of the detected disorders after CCT and skeletal trauma [10]. In paperwork [12], the activation of LPO in case of CCT is referred to one of the leading syndromes of traumatic disease. Other authors consider the activation of LPO to be the trigger for the development of the body's systemic response to inflammation [13].

The peculiarity of the dynamics of 8-isoprostane content in the blood serum of different age groups rats is the fact that the index reaches a maximum at the 7-th day with a subsequent decrease to the control level among immature rats, the maximum value of the index is noted after 7-14 days among mature rats, and the index reaches its maximum after 3 days and remains at the same level up to the 21-st day with a subsequent decrease that does not reach the control level among old rats. It should be added that at the maximum of growth, the highest content of 8-isoprostane in the blood serum was observed among immature rats, and the lowest – among old rats.

Thus, in response to trauma, which is standardized by the energy of the skull impact and the nature of the hip injury, the maximum increase in lipid peroxidation occurs after 7 days among immature rats. The amplitude of the increase in LPO in this experimental group is significantly higher than among rats of other age groups. Subsequently, the intensity of lipid peroxidation decreases rapidly, reaching control levels. This is apparently due to a greater oxygen need during the hypermetabolic phase and increased formation of AOS and free radicals, followed by mobilization of antioxidant defense, which will restore the serum 8-isoprostane content to the level of the control group [14]. At the same time, in response to trauma, the maximum increase in LPO occurs faster – after 3 days among old rats, but the amplitude of growth is smaller and longer in time (up to the 21st day), and the subsequent decrease in the serum content of 8-isoprostane does not reach the control level. Thus, in the body of old rats, the formation of prooxidant factors in response to trauma is less but is accompanied by a rapid decrease in the level of antioxidant defense and a lower ability of the body to restore it.

In order to level the age-related differences in the activity of lipid peroxidation among rats of different age groups, which already dominated among immature rats in the control, the average ratio of individual values of 8-isoprostane in the blood serum to the average value of the control group was calculated under the conditions of modeling of CST. This indicator allows to quantify the degree of increase or decrease of the studied index relative to the control. The analysis of the results showed that the increase in serum 8-isoprostane was significantly higher after 7 days among immature rats – during the period of early manifestations of traumatic disease. However, starting from the 21st day, the degree of increase of this indicator began to prevail in the group of old rats, and after 28 days the indicator was clearly higher in the groups of mature and old rats. The obtained results further confirm the fact that during the early manifestations of traumatic disease, the degree of increase in LPO dominates among immature rats. However, these disorders are within the limits of homeostatic regulation and the index decreases by the 28th day. At the same time, the degree of increase in the content of 8-isoprostane in the blood serum remains elevated during the late manifestations of traumatic injury among old rats,, indicating the insufficiency of the body's antioxidant systems and the need for their correction.

Under the conditions of the modeled trauma, the group of mature rats in terms of the content of 8-isoprostane and the degree of its increase in the blood serum occupies an intermediate position, which probably corresponds to the antioxidant and recovery capacity of this age group.

Thus, the conducted studies prove the role of age in determining the amplitude and time characteristics of the increase in the processes of lipid peroxidation in the body as one of the systemic manifestations of CST. The established age-related differences in the dynamics of 8-isoprostane concentration in the blood serum indicate the importance of an age-based approach to the choice of correction agents in the dynamics of traumatic disease, which requires further in-depth preclinical study.

Conclusions

1. The modeling of CST among rats of different age groups is accompanied by an increase in the intensity of lipid peroxidation processes, which is manifested by a significant increase in the content of 8-isoprostane in the blood serum. Among immature rats, the index reaches a maximum after 7 days (12.51 (10.93; 13.56) pg/ml), significantly exceeds other experimental groups and decreases by the 28th day, reaching the level of the control group (p=0.898). Among old rats, the maximum increase in lipid peroxidation occurs after 3 days of the experiment, characterized by the lowest amplitude of 8-isoprostane increase in the blood serum (6.10 (5.15; 6.83) pg/ml, remains at the same level up to the 21st day (p=0.702), followed by a decrease that is 1.48 times (4.56/3.08) higher than the control level (p=0.002).

2. During the early manifestations of traumatic disease, the degree of increase in the content of 8-isoprostane in the blood serum relatively to the control group prevails among immature rats, while during the late manifestations – among old rats.

3. Under the conditions of modeled trauma, the group of mature rats in terms of 8-isoprostane content in the blood serum and the degree of its increase relatively to the control group occupies an intermediate position, which corresponds to the antioxidant and regenerative capacity of this age group.

The prospect for further research is the selection and study of the effectiveness of antioxidants, taking into account the age-related amplitude and time characteristics of the increase in LPO under the influence of CST.

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