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The Result of Some Biomarker of Free Radical-Peroxidation of Lipids and Antioxidant System of Experimental Acute Infarction Model Induced by Coronary Artery Occlusion in Rats

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Abstract

Background: Recently years, Increasing coronary artery disease, diabetes, and cancer in the worldwide. Epidemiological studies indicate that *ischemic heart disease* will constitute the major disease-burden worldwide by the year 2020. Myocardial infarction is invariably followed by numerous pathophysiological and biochemical alterations including hyperlipidemia, thrombosis, lipid peroxidation and free radical damage etc., leading to qualitative and quantitative changes of myocardium. Determination of in blood serum and cardiac tissue homogenate levels of cardiac biomarker cardiac specific troponin I and estimation of lipid peroxidation products and some antioxidants enzymes of experimental acute infarction model induced by coronary artery occlusion in rats. Materials and methods: Adult male Wistar rats, weighting approximately 180 to 200±20 gram, used for the experiment. They were divided randomly into 2 groups (6-8 animals in each group). They were distributed as follow: first group (healthy, non treatment), second group (control, experimental acute infarction model induced by coronary artery occlusion in rats, non treatment). We did coronary occlusion induced myocardial ischemia by Kogan A.K., Ambaga M /1979/'s method.

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The experiment is 1st, 3rd, 7th, 14th 21st days blood samples were collected and used to determine in blood serum and cardiac tissue homogenate levels of cardiac biomarker cardiac specific troponin I (CT_n-I) and estimation of lipid peroxidation products (MDA, SA, LPO) and some antioxidants enzymes (SOD, GSH, GSH-px) were estimated using standard rat ELISA KIT by enzyme-linked immunesorbent assay. Result: Determination of cardiac troponin-I levels in blood serum of experimental acute infarction model induced by coronary artery occlusion in rats increased by 31.9-58.4% in the 1st, 3rd, 7th, 14th 21st days of the test compared to healthy groups. The cardiac biomarker cardiac specific troponin I is indicative for cardiomyocyte damage and is currently used in the diagnosis and prognosis of myocardial ischemia. Experimental acute infarction model induced by coronary artery occlusion in white rats, it is sufficiently shown that from day 1-21 MDA in plasma increased by 43.9 – 76.3%, plasma SA by 18.3-49.8% and LPO by 12.8-38.3%. This results in necrosis of cells and tissues, dissolving of membrane and stimulation of pathogenesis of disruption of membrane parts. It is also shown that substances such as endogen and antioxidant decreases in heart ischemia. Conclusion: Determination of increased level are lipid peroxidation products (MDA, SA, LPO, CT_n-I), and decreased level are antioxidants (SOD, GSH, GSH-px) in blood serum of experimental acute infarction model induced by coronary artery occlusion in rats, it seems to induced of pathogenesis of coronary disease and infarction myocardium while the accumulation of lipid product cause to damage the cell membrane.

Keywords: Myocardial infarction; Free radical-pereoxidation of lipids; Antioxidant; Coronary occlusion induced myocardial ischemia; Electron and proton conductance.

1. Introduction

Recently years, Increasing coronary artery disease, diabetes, and cancer in the worldwide [1,2]. It is a process of narrowing coronary arteries overtime involved at all stages of the atherosclerotic process, from lesion initiation to plaque rupture. Acute occlusion of the coronary artery by thrombosis could induce myocardial infarction (MI), and developed into heart failure eventually. In the past few years, inflammation has emerged as a major driving force of atherosclerotic lesion development [3]. Both MI and heart failure remain major causes of mortality and morbidity [4]. Epidemiological studies indicate that ischemic heart disease (IHD) will constitute the major disease-burden worldwide by the year 2020 [5]. For the first time, Russian researchers have found that free radical-peroxidation of lipids increases in infarction myocardium and IHD, according to Ambaga M, Kogan A.K, Kudrin A.N. Increased free radical-pereoxidation of lipids during heart ischemia and infarction myocardium cause lipids products accumulate and damage to cell membranes begin to involve in infarction myocardium. Full necrosis zone, which formed during 30 minutes after shortage of donators and acceptors, where occurred the complete stop of clockwise normal flow of electrons and protons is characterized by irreversible stop of electron and proton conductance [6]. Troponin complex is a component of skeletal and cardiac muscle thin filaments. It consists of three subunits troponin I, T, and C, and it plays a crucial role in muscle activity, connecting changes in intracellular Ca^{2+} concentration with generation of contraction. For the last 25 years cardiac isoforms of troponin I and T have been widely used for immunochemical diagnostics of pathologies associated with cardiomyocyte death (myocardial infarction, myocardial trauma, and others). This review summarizes the existing evidence on the structure and function of troponin complex subunits, their role in the regulation of cardiac muscle contraction, and their clinical applications [7]. It occurs when myocardial

ischemia surpasses the critical threshold level for an extended time, resulting in irreversible necrosis of the myocardium [8]. Myocardial infarction is invariably followed by numerous pathophysiological and biochemical alterations including hyperlipidemia, thrombosis, lipid peroxidation (LPO) and free radical damage etc., leading to qualitative and quantitative changes of myocardium [9]. It has also been suggested that oxidative stress produced by free radicals or reactive oxygen species (ROS), as evidenced by marked increase in production of lipid peroxidative products associated with decreased levels of antioxidants such as superoxide dismutase (SOD), catalase (CAT) and reduced glutathione (GSH), plays a major role in myocardial damage during MI [10,11]. We did coronary occlusion induced myocardial ischemia by Kogan A.K, Ambaga M. /1979/'s method. [12] Although a variety of surgical manipulations have been used during the past decade to induce the ischemic event, permanent left anterior descending artery (LAD) occlusion is the most common model used by researchers [13,14]. Nevertheless, this procedure is very time-consuming and associated with high surgery-related mortality, due at least in part to the trauma caused by mechanical ventilation and the large chest incision [15]. The rarity of comparative research of lipid oxidation intensity and antioxidant system to pathogenesis mechanism of coronary deficiency through cardiac troponin I, malondialdehyde, sialic acid, lipoperoxidase, superoxide dismutase, glutathione, glutathione peroxidase enzymeation around heart tissue homogenate and blood serum liquid (2 nd compartment) during the coronary artery disease of the experimental subject has become the basis of our research. Comparative study of estimating change in free radical-peroxidation of lipids and antioxidant system during the experimental acute infarction model induced by coronary artery occlusion in rats

2. Materials and methods

The experiment was conducted on "The innovation research, bio-modeling laboratory of New Medicine Medical University, ELISA laboratory of Hulj-Borjigon hospital". Adult male Wistar rats, weighting approximately 180 to 200±20 gram, were using for the experiment. The were divided randomly into 2 groups (6-8 animals in each group). They were distributed as follow: first group (healthy, non treatment), second group (control, experimental acute infarction model induced by coronary artery occlusion in rats, non treatment). All animals supplied with standard food during the experiment with an access of water. Experimental procuders were conducted in accordance with the regulations of Animal Ethical committee. We did coronary artery occlusion induced myocardial ischemia by *Kogan A.K., Ambaga M. /1979/*'s method [12]. On white rat with, we started sleeping with ketamine hydrochloride, and have secured rat to immobile which after attached rat to ventilator. We have maintained experimental animal body temperature between 36.7-37^{o}C and reinforced immobile rat to surgery table. With help of laryngoscopy, we have introduced polyethylene tube to trachea, and attached it to ventilator (Small Animal ventilator R407 RWD Life Science/ and have ventilated 112-114/min, 1.8-2.0 cc volume and performed surgical procedure in aseptic condition with help of surgical headlight. left descending artery (LAD) occlusion: To perform a thoracotomy at the left side the rat is relocated on its right side. The skin is incised and the subcutaneous tissue is dissected free, the ventral serrated muscle of thorax and the intercostal muscles are transected. The thorax is incised in the third intercostal. The opening is widened with a rip retractor. The lung is displaced with the help of visualize the left auricle, at whose tip the left anterior descending artery takes course toward the apex of the heart. Before occlusion it is essential to open carefully the pericardium. Did coronary artery occlusion induced myocardial ischemia, to bind the wound. Estimation of lipid peroxidation

products and antioxidants:

The experiment is 1st, 3rd, 7th, 14th 21st days blood samples were collected and used to determine the serum and cardiac tissue homogenate levels of cardiac biomarker cardiac specific troponin I in (CT_n-I), malondialdehyde (MDA), sialic acid (SA), lipoperioxidase (LPO), superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GSH-px) were estimated using standard rat ELISA KIT by enzyme-linked immunesorbent assay (Shanghai MLBIO Biotechnology Co.Ltd, China).

3. Results

The experiment is 1st, 3rd, 7th, 14th 21st days blood samples were collected and used to determine in blood serum and cardiac tissue homogenate levels of cardiac biomarker cardiac specific troponin I (CT_n-I) and estimation of lipid peroxidation products (MDA, SA, LPO) and antioxidants (SOD, GSH, GSH-px) were estimated using standard rat ELISA KIT by enzyme-linked immunesorbent assay.

Table 1: The levels of cardiac biomarker cardiac specific troponin I (CT_n-I) of experimental acute infarction model induced by coronary artery occlusion in rats

№	Days of experiment, group (s)	CTn-I (ng/L)	
		Healthy	Control
1	1 day	11.16±0.361	26.84±0.871*
2	3 day	12.85±0.192	22.95±1.137*
3	7 day	12.66±0.235	21.12±0.741*
4	14 day	12.4±0.32	18.22±0.436*
5	21 day	11.98±0.32	21.55±0.629*

*- When compared control group measurements with healthy group $P \leq 0.05$, $P \leq 0.001$

As shown in Table 1, Determination of CTn-I concentration in cardiac tissue homogenate of control group (experimental acute infarction model induced by coronary artery occlusion in rats) animals had increased 31.9-58.4% during 1-21 days, and have been maintained stable during either acute and chronic stage ($P \leq 0.001$). The cardiac biomarker cardiac specific troponin I is indicative for cardiomyocyte damage and is currently used in the diagnosis and prognosis of myocardial ischemia.

This indicates that the coronary artery disease or myocardial infarction (cardiac muscle necrosis) causes dysfunction in the interaction between actin and myosin of heart muscle during the heart ischemia and decomposed heart muscle cells becoming dead cell making the decaying area bigger.

Table 2: The result of some biomarker of lipid peroxidation products of experimental acute infarction model induced by coronary artery occlusion in rats

№	Days of experiment, group (s)		MDA (nmol/L) in serum	SA (ng/L) in serum	LPO (nmol/L) in cardiac tissue homogenate
1	1 day	Healthy	0.87±0.043	18.51±0.27	38.23±1.078
		Control	1.829±0.017*	22.68±0.232*	62.03±0.854*
2	3 day	Healthy	0.68±0.026	17.8±0.351	37.65±0.380
		Control	2.88±0.185*	21.94±1.186*	52.16±1.209*
3	7 day	Healthy	0.75±0.18	18.31±0.52	38.11±0.486
		Control	1.41±0.046*	29.87±1.012*	45.48±0.872*
4	14 day	Healthy	0.83±0.12	17.04±0.3	36.29±0.29
		Control	1.48±0.110*	33.98±0.553*	41.65±0.487*
5	21 day	Healthy	0.79±0.041	18.26±0.31	38.38±0.22
		Control	1.97±0.057*	31.44±2.193*	44.12±0.964*

*- When compared control group measurements with healthy group $P \leq 0.05$, $P \leq 0.001$

As shown in Table 2, Determination of malondialdehyde levels in blood serum of experimental acute infarction model induced by coronary artery occlusion in rats increased by 43.9-76.3% in the 1-21 days of the test compared to healthy groups. Have been maintained stable during either acute and chronic stage ($P \leq 0.001$). Concluding from this increase, it is observed that high concentrations of intermediate oxidation product accumulated around the blood and plasma causes the dysfunction in the normal flow of electron and proton in cell breathe cycle which causes the stimulation of oxidation during the reaction of a lot of clear NADH and FADH during both in acute and chronic phase of heart ischemia matches with the research result of foreign researchers. As shown in Table 2, Determination of sialic acid in blood serum concentration of control group (experimental acute infarction model induced by coronary artery occlusion in rats) animals had increased by 18.3-49.8% during 1-21 days of the test compared to healthy groups ($P \leq 0.001$). Considering the increase in sialic acid in the subject group, over stimulation of oxidant in two cell layers of the membrane during the heart ischemia caused the separation of glycoprotein parts such as sialic acid which is part of membrane structure and increased it around the plasma. As shown in Table 2, Determination of lipoperioxidase levels in cardiac tissue homogenate of experimental acute infarction model induced by coronary artery occlusion in rats increased by 12.8-38.3% in the 1-21 days of the test compared to healthy groups. Have been maintained stable during either acute and chronic stage ($P \leq 0.001$). It can be seen that the amount of lipid peroxidation which takes part in the forming of oil bodies increases in day 1 and 3 of the test from this increase. Also from the increase in health value in all days of the test, it's been proven that lipid peroxidation enzyme takes a lead role in the process of high level of active oxygen stipulated with heart ischemia causing the strong stimulation of oxidation in heart tissue and cells which leads into the forming of oxidation oil bodies from unsaturated fatty acids that creates two

layers of membrane and continuation of oxidation chain cycle.

Table 3: The result of some biomarker of antioxidant of experimental acute infarction model induced by coronary artery occlusion in rats

№	Days of experiment, group (s)	SOD (pg/ml)			
		1 day	3 day	14 day	21 day
1	Healthy	7.96±0.22	8.21±0.09	7.74±0.05	7.69±0.18
2	Control	5.78±0.23*	5.58±0.27*	3.49±0.14*	4.68±0.18*

*- When compared control group measurements with healthy group P≤ 0.05, P≤ 0.001

As shown in Table 3, During 1-21 days of experiment, non-treatment control group cardiac tissue homogenate superoxide dismutase enzyme concentration activity have decreased by following sequence of 27.38%, 32.03%, 54.9%, 39.1% (P≤0.001). The decrease shows that during the coronary artery disease over oxidation process would be strongly stimulated and that leads to the high consumption rate of endogen and antioxidant. Also, the decrease in the true value of statistics shows that during the acute and chronic insufficiency of oxygen, the normal flow of electron and proton in heart tissue and cell gets disrupted and insufficiency in high energy compounds such as ATP and NADPH around the area of mitochondrial membrane leads into overstimulation of oxidant which causes drastically high consumption rate of endogen antioxidant enzymes such as catalase, superoxide dismutase, vitamin E, and glutathione peroxidase.

Table 4: The result of glutathione of experimental acute infarction model induced by coronary artery occlusion in rats

№	Days of experiment, group (s)	GSH (ng/L)				
		1 day	3 day	7 day	14 day	21 day
1	Healthy	150.22±2.488	145.81±1.935	151.08±1.374	147.93±0.71	149.23±1.155
2	Control	128.40±2.68*	113.38±5.873*	123.05±2.993*	112.42±2.805*	126.94±2.471*

*- When compared control group measurements with healthy group P≤ 0.05, P≤ 0.001

As shown in Table 4, During 1-21 days of experiment, determination of glutathione levels in cardiac tissue homogenate of experimental acute infarction model induced by coronary artery occlusion in rats decreased by following sequence of 14.5%, 22.2%, 18.5%, 24%, 14.9% of the test compared to healthy groups, p≤0.001. Comparing the healthy groups to subject group, a decrease in the source of clear glutathione shows that during the heart ischemia over-oxidation of fatty substances gets strongly stimulated and free radicals in the heart cell increase significantly. Following this phenomenon, the protection system from endogen antioxidant gets fully mobilized which allows the condition of decreasing clear compounds such as glutathione. According to this

result, during the acute and chronic heart ischemia in the white rat, many pathogenesis phenomena appear in the heart tissue and cells phase by phase followed by processes such as insufficiency of oxygen stipulated by ischemia, over-oxidation of fatty substances, high rate of fat hydroperoxide, mobilization of antioxidant enzymes, and over-consumption of clear compounds used to stabilize over-oxidation such as clear glutathione. Therefore, it may be assumed that the number of clear compounds during the acute ischemia is decreasing in the heart tissue.

Table 5: The result of glutathione perioxidase of experimental acute infarction model induced by coronary artery occlusion in rats

№	Days of experiment, group (s)	GSH-Px (pmol/ml)	
		Healthy	Control
1	7 day	5.18±0.16	2.21±0.121*
2	14 day	5.66±0.01	2.21±0.11*
3	21 day	6.01±0.094	2.19±0.136*

*- When compared control group measurements with healthy group P≤ 0.05, P≤ 0.001

As shown in Table 5, Determination of glutathione perioxidase levels in blood serum of experimental acute infarction model induced by coronary artery occlusion in rats decreased by 57.3-63.5% in the 7-21 days of the test compared to healthy groups p≤0.001. Decrease during the duration of the test shows that stopping the new production of toxic radicals and nitrogen over-oxidation activity of the glutathione peroxide enzyme cell is decreasing. Also, it shows that during both acute and chronic coronary artery disease, over stimulation of fatty oxidant and accumulation of toxic fatty hydrogen peroxide around the tissue and cell causes high need of antioxidant containing seen arises. For example, in the case of experimental acute infarction model induced by coronary artery occlusion in rats, for the untreated subject group MDA and LPO on the 1st day r=+0.45, on 3rd day r=+0.42, on 14th day r=+0.56, on 21st day r=+0.27, also between SA and LPO r=+0.40, for between MDA and SOD on the 1st day r=+0.44, between SOD and SA r=+0.33, thus proving the test above.

4. Discussion

Recently years, Increasing cardiovascular diseases, diabetes, and cancer in the whole world. An estimated 17.9 million people died from cardiovascular deseases in 2016, representing 31% of all global deaths. Of these deaths, 85% are due to heart attack and stroke, reported WHO [2]. For our research, we identified serum and heart tissue substances in severe, acute and chronic phase of coronary artery disease and did comparative study with other researchers' research. It has been proven that during the heart ischemia, intensified fat oxidation process accumulates in the oil oxidation and damaging heart muscle cell membrane, further involving in pathogenesis of the heart attack (Ambaga M, Kogan A.K, Kudrin A.N. 1984) [12]. The most unique heart biomarker that identifies the heart muscle cell's damage or necrosis is cardiac troponin I protein and it is still

used in identifying heart attack caused by insufficient blood flow and identifying the seriousness of the cause (Tallaj JA, Franco V, Rayburn BK and his colleagues 2005) [16]. After injecting the cardiac troponin I into the both healthy and subject group in 1st, 3rd, 7th, 14th 21st days after creating the coronary artery disease in test experiment, the statistics increased 31.9-58.4% positive. Also it indicates that during the severe, acute and chronic phase, expansion of necrosis area around the heart muscle matches with the result of previous researchers. Some of the researchers noted that effects of catecholamine cause change in fat substances and structure of biological membrane. Significant increase in fat-free acids and decrease in phospholipids results in membrane dysfunction causing loss of permeability and flexibility of the membranes, decrease of membrane ion and enzyme process becomes the main source for heart cell's damage, ischemia and heart attack risk (Yeagle.,1985). Heart cell's phospholipids metabolites are the primary source to heart failure and ischemia (Mathew and his colleagues 1981). Researchers also noted that lack of enzymes such as catalase and superoxide dismutase can cause harmful effects on the healthy cells or tissue [17]. Based on the above-mentioned materials and our results of research, it is proven that during the coronary artery disease in malondialdehyde, sialic acid that indicates intensifying of peroxidation lipids and membrane damage and lipoperoxidase enzyme that conditions chain cycle of fat oxidation are stimulated in tissue and serum level. On the other hand, stimulation of superoxide dismutase, glutathione, and glutathione peroxide enzymes that indicates body protection system endogen and antioxidant decreases in tissue and serum level which results in stimulation of some pathogenesis mechanism of coronary artery disease that further destroys cell and tissue.

5. Conclusion

1. Determination of increased level are lipid peroxidation products (MDA, SA, LPO), and decreased level are antioxidants (SOD, GSH, GSH-px) in blood serum of experimental acute infarction model induced by coronary artery occlusion in rats, it seems to induced of pathogenesis of coronary disease and infarction myocardium while the accumulation of lipid product cause to damage the cell membrane.
2. During the cell damage of coronary artery disease, intensified cell membrane lipid oxidation, per oxidant produced from cell membrane and fat acid oxidation increases dramatically around serum level which highly stimulates the chain cycle of lipid oxidation process. It is shown from our research that this process becomes one of the main pathogenesis during the acute and chronic ischemia and infract of coronary artery disease.

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