Free Radical Lipid Peroxidation during Amiodarone Therapy for Postinfarction Cardiosclerosis

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Postinfarction remodeling of the heart in animals with myocardial infarction was accompanied by activation of lipid peroxidation in myocardial tissue and blood serum and decrease in antioxidant enzyme activity. In animals with postinfarction cardiosclerosis treated with amiodarone, we observed decreased accumulation of lipid peroxidation products and normalization of superoxide dismutase activity.

Key Words: *lipid peroxidation; amiodarone; postinfarction cardiosclerosis*

The development of postinfarction cardiosclerosis (PICS) is accompanied by structural and electrophysiological remodeling of the myocardium. Electrophysiological remodeling of the myocardium is a complex of molecular, metabolic, and ultrastructural changes in cardiomyocytes, which determines electrophysiological dysfunction of the heart and development of arrhythmias [5]. These features contribute to high risk of paroxysmal arrhythmias and sudden cardiac death in the postinfarction period [4]. Myocardial infarction and PICS are followed by activation of free radical processes in the myocardium [8,11], which impairs the integrity of cardiomyocyte membranes and causes dysfunction of Ca^{2+}-ATPase. These processes result in contractile dysfunction and change in energy supply to the myocardium [9,2]. Variations in intracellular energy metabolism are accompanied by changes in Na^+, K^+, and Ca^{2+} currents and, therefore, disturbances in automatism and conduction in cardiac cells [2].

Class III antiarrhythmic drugs are widely used for the correction of cardiac arrhythmias. One of these drugs is amiodarone (Cordarone). Amiodarone is used in clinical practice for the treatment of severe arrhythmias [10]. Multicenter, randomized, placebo-controlled trials (CAMIAT and EMIAT) showed that amiodarone therapy significantly decreased the risk of arrhythmic and cardiac death in postinfarction patients with ventricular extrasystoles [11,13]. Much recent attention is paid to the mechanisms for action of amiodarone on ischemic myocardium during PICS.

Here we studied the intensity of lipid peroxidation (LPO) in myocardial tissue and blood serum from rats with PICS, which received the course of amiodarone therapy.

MATERIALS AND METHODS

Experiments were performed on 30 Wistar rats weighing 180-200 g. Groups 1 (control 1) and 2 (control 2) consisted of sham-operated animals and rats with PICS, respectively. Group 3 animals with PICS receiving amiodarone.

The development of cardiosclerosis in group 2 and 3 rats was triggered by myocardial infarction caused by coronary occlusion [12]. Thoracotomy was performed in ether-anesthetized animals under sterile conditions. A ligature was applied to the upper third of the left descending coronary artery.

The surgical wound was sutured. The animals were maintained in a vivarium for 45 days under standard conditions. PICS was observed by the end of this period.

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Distilled water was administered through a gastric tube to group 1 and 2 rats (twice a day, 14 days) starting from the 30th day after surgery. Group 3 animals intragastrically received amiodarone in a dose of 10 mg/kg (daily dose 20 mg/kg).

Control and treated animals were examined after 45 days. Blood samples were centrifuged at 3000 rpm for 5 min. Serum aliquots were stored in liquid nitrogen. The samples of myocardial tissue were taken.

The intensity of LPO in blood serum and myocardial tissue was estimated from the contents of conjugated dienes (CD) [3] and malonic dialdehyde [6] and activities of antioxidant enzymes superoxide dismutase [1] and catalase [7].

The results were analyzed by paired Student's *t* test. The differences were significant at $p<0.05$.

RESULTS

Postinfarction remodeling of the myocardium in group 1 animals was accompanied by pronounced activation of free radical processes in the myocardial tissue. The contents of CD and MDA in myocardial homogenates from PICS rats were higher than in sham-operated animals (by 1.3 and 1.8 times, respectively; Table 1).

The development of PICS in rats was accompanied by an increase in the contents of MDA and CD in blood serum (by 22 and 90%, respectively, compared to sham-operated animals; Table 2). These changes reflect activation of LPO during postinfarction remodeling of the myocardium.

The course of intragastric administration of amiodarone for 2 weeks was followed by a decrease in CD content in the myocardium of group 3 rats compared to group 2 animals. MDA content in group 3 rats was lower than in group 2 animals. However, MDA content in group 3 rats remained higher than in sham-operated animals.

Similar inhibition of LPO was also observed in blood serum of group 3 rats. Amiodarone decreased the contents of MDA and CD in group 3 animals by 37 and 59%, respectively, compared to group 2 rats (Table 2).

These data show that the course of intragastric administration of amiodarone decreased accumulation of LPO products in PICS animals. These changes probably contribute to the antiarrhythmic effect during postinfarction remodeling of the myocardium.

Components of the endogenous antioxidant system are the major factors for cell protection from reactive oxygen species and lipid hydroperoxides. Therefore, the effectiveness of myocardial recovery after coronary disease can be estimated from antioxidant enzyme activity in the myocardium and blood serum of animals with postinfarction remodeling of the myocardium. The effect of amiodarone on the antioxidant system under these conditions is also of considerable diagnostic significance.

Measuring of antioxidant enzyme activity in myocardial samples and blood serum from animals with PICS showed that the development of cardiosclerosis was accompanied by a significant decrease

TABLE 1. Effect of the Course of Amiodarone Administration on the Content of LPO Products and Antioxidant Enzyme Activity in the Myocardium of Rats with PICS (*M*±*m*)

Group	CD, ΔE_{232}/g tissue	MDA, nmol/g tissue	Catalase, mmol/g protein/min	SOD, mmol/mg protein/min
1	0.32±0.03	9.48±0.85	30.23±2.64	0.87±0.04
2	0.43±0.04*	16.63±0.97**	18.10±1.07**	0.09±0.01***
3	0.34±0.03^{+}	11.23±0.89^{**++}	21.31±1.06^{**++}	0.19±0.01^{**++}

Note. Here and in Table 2: *$p<0.05$, **$p<0.01$, and ***$p<0.001$ compared to group 1; $^{+}p<0.05$ and $^{++}p<0.01$ compared to group 2.

TABLE 2. Effect of the Course of Amiodarone Administration on LPO and Antioxidant Enzyme Activity in Blood Serum from Rats with PICS (*M*±*m*)

Group	CD, ΔE_{232}/g tissue	MDA, nmol/g tissue	Catalase, mmol/g protein/min	SOD, mmol/mg protein/min
1	1.03±0.08	20.99±2.03	20.52±1.63	0.86±0.05
2	1.96±0.09*	25.58±2.26**	15.92±0.95**	0.09±0.01***
3	1.17±0.12^{+}	19.22±1.31^{++}	11.48±0.64^{***++}	0.24±0.02^{***++}

in catalase and SOD activities (compared to sham-operated animals; Tables 1 and 2).

The decrease in SOD and catalase activities during experimental cardiosclerosis is probably related to inhibition of their active centers by fatty acid peroxides. The formation of these compounds increases in myocardial ischemia [9]. On the other hand, the decrease in antioxidant enzyme activity induced by various factors contributes to the increased formation of LPO products, which is mediated by the feedback mechanism.

Activities of catalase and SOD in the myocardium of group 3 animals increased compared to those in group 2 rats (Table 1). However, antioxidant enzyme activity in these animals remained lower than in sham-operated rats.

Serum activities of catalase and SOD in animals with experimental cardiosclerosis were also lower than in sham-operated rats.

SOD activity in group 3 rats was higher than in group 2 animals (Table 2). At the same time, catalase activity decreased in group 2 rats. The mechanism underlying the decrease in serum catalase activity remains unclear and requires further investigation.

Our results indicate that experimental postinfarction remodeling of the heart is accompanied by activation of LPO and decrease in antioxidant enzyme activity in myocardial tissue and blood serum. The course of amiodarone administration in a daily dose of 20 mg/kg was followed by a decrease in the contents of MDA and CD in myocardial tissue and blood serum and contributed to the increase in SOD and catalase activities. Amiodarone-induced decrease in LPO during postinfarction cardiac remodeling is associated with the effect of the test drug on ion transport in myocardial cells. These changes promote normalization of the heart rate and decrease in oxygen demands of the myocardium. Published data show that administration of amiodarone to animals with dilated cardiomyopathy has a cardioprotective effect. This drug prevents irreversible degeneration of cardiomyocytes, improves the dynamics of oxidation-reduction enzyme activities, and normalizes bioelectric activity of the heart and total content of adenyl nucleotides [12]. Amiodarone probably has a similar effect under conditions of PICS and contributes to inhibition of LPO.

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