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Chronic Administration of Coenzyme Q_{10} Limits Postinfarct Myocardial Remodeling in Rats

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Abstract—The effect of chronic coronary artery occlusion on the content of rat myocardial coenzymes Q (CoQ) and evaluation of the applicability of CoQ_{10} for limiting postinfarct remodeling have been investigated. Left ventricle myocardium hypertrophy was characterized by the decrease in CoQ_9 (−45%, $p < 0.0001$), CoQ_{10} (−43%, $p < 0.001$), and α-tocopherol (−35%, $p < 0.05$). There were no differences between the parameters of postinfarction and sham-operated rats in plasma. Administration of CoQ_{10} (10 mg/kg) via a gastric probe for 3 weeks before and 3 weeks after occlusion maintained higher levels of CoQ in the postinfarction myocardium: the decrease in CoQ_9 and CoQ_{10} was 25% ($p < 0.05$) and 23% ($p < 0.05$), respectively (versus sham-operated animals). Plasma concentrations of CoQ_{10} were more than 2 times higher ($p < 0.05$). In CoQ treated rats there was significant correlation between plasma levels of CoQ and the infarct size: $r = -0.723$ ($p < 0.05$) and $r = -0.839$ ($p < 0.01$) for CoQ_9 and CoQ_{10}. These animals were also characterized by earlier and more intensive scar tissue formation in the postinfarction myocardium and also by more pronounced cell regeneration processes. This resulted in the decrease in both the infarct size (16.2 ± 8.1 vs. 27.8 ± 12.1%) and also mass index of left ventricle (2.18 ± 0.24 vs. 2.38 ± 0.27 g/kg) versus untreated rats ($p < 0.05$). Thus, long-term treatment with ubiquinone increases plasma and myocardial CoQ content and this can improve the survival of myocardial cells during ischemia and limit postinfarct myocardial remodeling.

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Key words: coenzyme Q, ischemia, infarct, myocardium, hypertrophy, HPLC, cardioprotection

During the last decade there have been an increased number of studies on the role of oxidative stress in pathogenesis of cardiovascular diseases [1] and also mechanisms of action and perspectives for use of antioxidants [2, 3]. Such common diseases as hypertension, ischemic heart disease, and heart failure are accompanied by myocardial hypertrophy, which is an important component for myocardial remodeling processes. Increased production of free radicals in the hypertrophied myocardium [4-7] implies corresponding changes in the antioxidant defense system. In most studies, myocardial antioxidant status was evaluated by the level of pro- and/or antioxidant enzymes [8-10]. The role of low molecular weight antioxidants, coenzyme Q (CoQ) and α-tocopherol, in pathogenesis of cardiovascular diseases remains unclear.

Coenzyme Q, ubiquinone, has many biochemical functions [11]. It is involved in transformation of energy as an important component of oxidative phosphorylation in mitochondria. Coenzyme Q stimulates cell growth and attenuates cell death. Ubiquinone is the most important fat-soluble antioxidant. In all membranes, the antioxidant effect of ubiquinone consists in direct interaction of its reduced form with free radicals (lipid radicals, hydroxyl radical, peroxynitrite) or in regeneration of α-tocopherol (vitamin E) and ascorbate. These properties of CoQ limit lipid peroxidation in biomembranes and protect DNA and proteins against the damaging effect of free radicals.

Study of the role of ubiquinone in pathogenesis of cardiovascular diseases means evaluation of its tissue levels depending on manifestations of pathological changes. However, only a few studies meet this criterion.

Thus, in this study we have investigated changes in coenzyme Q content in rat myocardium induced by chronic occlusion of the coronary artery and efficiency of long term administration of coenzyme Q_{10} (before and after occlusion) for limitation of postinfarction myocardial remodeling.

Abbreviations: CoQ) coenzyme Q; LV) left ventricle; RV) right ventricle.

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MATERIALS AND METHODS

Experimental animals and surgical operations. Male Wistar rats of 250-300 g were used in this study.

The task of the first series of experiments was to evaluate whether myocardial infarction is accompanied by exhaustion of myocardial CoQ content. Rats were subdivided into two groups. Under sterile conditions, intraperitoneal anaesthesia (Nembutal, 50 mg/kg, intraperitoneally), and artificial lung ventilation of animals of the first group ($n = 8$) were subjected to chronic occlusion of the descending branch of the left coronary artery at the level of auriculum of the left atrium. The second group of sham-operated rats ($n = 8$) underwent all the same treatments except ligation of the coronary artery did not cause obstacles for coronary blood circulation. After three weeks of the postoperation period, the rat heart ventricles were weighed and the indexes of masses of left ventricle (LV) and right ventricle (RV), representing ratio of ventricle mass to animal body mass (g/kg) were calculated. The infarction zone of the LV was calculated planimetrically as ratio of area of the outer surface of the infarction zone to the whole area of the LV myocardium (%).The infarction zone was excised and remaining myocardium was frozen and kept at −20°C for quantitative analysis of CoQ.

In the second series of experiments, we evaluated the effectiveness of long-term pretreatment of animals with CoQ_{10} as a cardioprotector. Coenzyme Q_{10} was administered *per os* using a mode increasing both its plasma and myocardial levels [12, 13]. Three groups of rats were used. Animals of the first group received the solubilized form of CoQ_{10} (Kudesan; Aqua-MDT, Moscow) in the daily dose of 10 mg/kg via a gastric probe for 3 weeks before and 3 weeks after occlusion. The preparation also contained α-tocopherol (daily dose 1.5 mg/kg). Rats of the second group received an equivalent volume of saline for 3 weeks before and 3 weeks after occlusion. Animals of the third group were sham-operated. Three weeks after the operation (and at least 18 h after the last administration of the cardioprotector), 1 ml of blood was collected from the femoral artery of the narcotized rats for analysis of CoQ and α-tocopherol in plasma. The infarction zone and mass indexes of RV and LV were evaluated as described above. Small samples of non-infarct myocardium of the LV were used for a morphological study.

Morphological study. Samples of LV from all rats employed in the second series of experiments (including myocardial samples from the non-infarction zone of rats of the first and the second groups) were analyzed by light and electron microscopy. Samples were prepared using a traditional method [14]. Tissue samples cut into pieces of 1 mm^3 were fixed in 2.5% glutaraldehyde in phosphate buffer (pH 7.0) followed by subsequent fixation in 1% osmium tetroxide for 2 h. The material was embedded into Epon-araldite resin. Semi-thin slices (1-1.5 μm) were analyzed using a Leitz light microscope (Germany). Ultra-thin slices (60-70 nm) were investigated using a Philips CM-10 electron microscope (Holland).

Quantitative analysis of coenzymes Q and α-tocopherol. Plasma and myocardial levels of α-tocopherol, CoQ_9, and CoQ_{10} were analyzed as described [15] with some modifications. Myocardium was cut and then homogenized in distilled water (1 : 4 w/v). The homogenate was centrifuged at 700*g* for 5 min to sediment unbroken cells and cell debris; supernatant was used for extraction of CoQ_9, CoQ_{10}, and α-tocopherol. Supernatant (100 μl) or blood plasma (100 μl) were mixed with 200 μl ethanol and 550 μl *n*-hexane, shaken for 10 min, and centrifuged at 3000*g* for 3 min. The layer of *n*-hexane (500 μl) was taken and the remaining portion was mixed with 550 μl of *n*-hexane and the extraction procedure was repeated again. A pooled extract was evaporated to dryness; dry residue was dissolved in 100 μl of ethanol. CoQ_9 and CoQ_{10} were reduced by adding 10 μl of 5% sodium tetrahydroborate in ethanol. An aliquot of the reduced extract (10 μl) was analyzed by high performance liquid chromatography using electrochemical detection (Coulochem II electrochemical detector). HPLC equipment (pump 580) was from Environmental Sciences Associate, Inc. (USA). Separation was carried out in the isocratic mode using a C18 (5 μm) column (150 × 4.6 mm) at a flow rate of 1.3 ml/min. The mobile phase contained 0.3% NaCl in the mixture ethanol–methanol–7% $HClO_4$ (970 : 20 : 10). Electrochemical detection was carried out using an analytic cell (model 5011) at voltage of −50 and +350 mV at the first and the second pairs of electrodes. Retention times for α-tocopherol, CoQ_9, and CoQ_{10} were 3.2, 6.5, and 8.5 min, respectively. Registration and analysis of chromatographic data employed a computer program supplied by Environmental Sciences Associate, Inc.

Statistical analysis. Results represent mean ± standard deviation. Statistical differences between groups were evaluated using the *t*-test.

RESULTS

Size of infarction and mass indexes of LV and RV. The chronic occlusion of coronary arteries caused formation of the infarct zone (26.2 ± 9.6% in the first series of experiments and 27.8 ± 12.1% in the second series of experiments) and development of hypertrophy of the LV. The index of LV mass was 2.28 ± 0.17 g/kg in the first series of experiments ($p < 0.02$ vs. 2.13 ± 0.18 g/kg in sham-operated animals) and 2.38 ± 0.27 g/kg in the second series of experiments ($p < 0.0001$ vs. 1.92 ± 0.13 g/kg in sham-operated rats). Results of the two series of experiments showed that LV infarction has a minor influence on the index of RV mass (0.84 ± 0.11 and 0.69 ± 0.23 g/kg in the postinfarct rats and 0.74 ± 0.09 and 0.59 ± 0.15 g/kg in sham-operated rats of the first and the second series, respectively).

Content of CoQ_9, CoQ_{10}, and α-tocopherol in left ventricle myocardium and plasma of rats of different experimental groups

Content	Sham-operated rats	Postinfarct untreated rats	Postinfarct CoQ_{10}-treated rats
Left ventricle myocardial content, μg/g wet weight	(n = 7)	(n = 12)	(n = 10)
CoQ_9	129.5 ± 23.8	71.6 ± 27.4*	100.3 ± 23.0$^{\#}$ **
CoQ_{10}	7.26 ± 1.5	4.16 ± 1.65*	5.39 ± 1.41$^{\#}$ ***
α-tocopherol	0.82 ± 0.19	0.49 ± 0.37***	0.33 ± 0.18*
Plasma content	(n = 7)	(n = 12)	(n = 7)
CoQ_9, ng/ml	291.4 ± 63.7	246.0 ± 66.6	380.6 ± 149.9
CoQ_{10}, ng/ml	15.2 ± 5.3	14.4 ± 3.64	40.5 ± 22.0$^{\#}$ ***
α-tocopherol, μg/ml	1.9 ± 0.57	1.5 ± 0.49	2.13 ± 0.20$^{\#\#}$
LV CoQ_9/CoQ_{10}	18.0 ± 1.5	18.5 ± 1.6	18.8 ± 1.7
Correlation coefficient, LV CoQ_9 vs. CoQ_{10}	0.911 ($p < 0.01$)	0.985 ($p < 0.01$)	0.952 ($p < 0.01$)

* $p < 0.001$ versus sham-operated rats.
** $p < 0.01$ versus sham-operated rats.
*** $p < 0.05$ versus sham-operated rats.
$^{\#}$ $p < 0.05$ versus postinfarct untreated rats.
$^{\#\#}$ $p < 0.01$ versus postinfarct untreated rats.

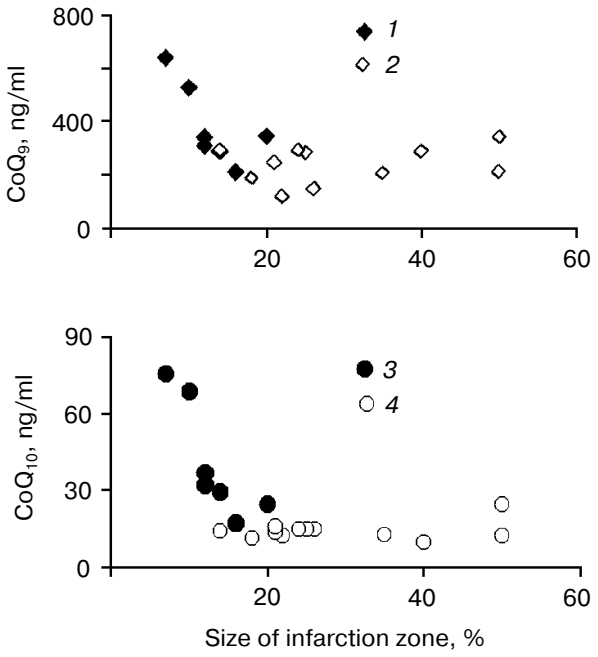

Fig. 1. Dependence between the size of infarction zone and plasma levels of CoQ_9 (*1*) ($r = -0.723$, $p < 0.05$) and CoQ_{10} (*3*) ($r = -0.839$, $p < 0.01$) in the group of postinfarction rats treated with CoQ_{10} 3 weeks before and 3 weeks after coronary artery occlusion. No correlation was found between the size of the infarction zone and plasma levels of CoQ_9 (*2*) and CoQ_{10} (*4*) in the group of untreated postinfarction rats.

Rats treated with CoQ_{10} were characterized by a smaller size of infarction (16.2 ± 8.1%) and LV hypertrophy (2.18 ± 0.24 g/kg) ($p < 0.05$) than untreated rats.

Levels of CoQ_9, CoQ_{10}, and α-tocopherol in blood plasma and myocardium. Results of the first series of experiments showed that CoQ content in the RV from postinfarction and sham-operated rats did not differ. Reduction by CoQ_9 (by 53%, $p < 0.05$) and CoQ_{10} (by 52%, $p < 0.05$) was typical for hypertrophied myocardium of the LV.

The second series of experiments also demonstrated exhaustion of antioxidant resources in hypertrophied LV myocardium (table). Mean values of CoQ_9 and CoQ_{10} were lower by 45% ($p < 0.0001$) and 43% ($p < 0.001$), respectively. The level of α-tocopherol was lower by 35% ($p < 0.05$). In blood plasma, there were no significant differences in the content of these antioxidants in postinfarction and sham-operated rats.

Rats treated with CoQ_{10} and α-tocopherol were characterized by more than 2-fold increase in blood plasma CoQ_{10} ($p < 0.05$), 13% increase in α-tocopherol; the increase in CoQ_9 did not reach statistical significance in comparison with untreated rats. In LV myocardium of the treated rats, concentrations of CoQ_{10} and CoQ_9 were significantly higher (by 31 and 40%, respectively, $p < 0.05$), whereas α-tocopherol level remained unchanged (table).

In the treated rats, there was negative correlation between plasma levels of CoQ_9 ($r = -0.723$, $p < 0.05$),

CoQ_{10} ($r = -0.839$, $p < 0.01$) and the size of the infarction zone (Fig. 1). In untreated postinfarction rats, values of infarction size and the index of LV mass did not depend on CoQ levels either in myocardium or in plasma. No correlation between levels of α-tocopherol in blood plasma or myocardium and the degree of ischemic myocardial damage was recognized.

Morphological study. *Light microscopy*. The light microscopy study of the postinfarction rat myocardium revealed destructive damages: breaks of myofibrils, cell disconnection, and increase in intercellular space. Breaks of cell membranes were accompanied by release of intracellular organelles into the extracellular space and in some cases myocyte nuclei were found outside cells. There were myofibril disorganization and loss of cell cross-striation. Cell disconnection was combined with "fusion" of myofibrils into large layers (representing conglomerates with indistinguishable borders between separate cells) with large solitary nuclei. These observations together with an increased size of remaining cardiomyocytes and their polymorphous nuclei reflect compensatory hypertrophy of the myocardium. Fibroblasts and various amounts of collagen fibrils found near (especially large) vessels suggested formation of scar tissue. Sizes of some fibroblasts were quite large; this suggested involvement of myocardial stroma in the process of hypertrophy.

Myocardium of rats treated with CoQ_{10} and subjected to experimental myocardial infarction was characterized by the same destructive changes as the postinfarction myocardium of untreated rats. However, there were many more foci of connective tissues formed by fibroblasts, and these foci were larger than in myocardium of untreated rats. This suggests earlier and intensive substitution of necrotic foci (and all damages) with connective tissue, transforming into a scar.

Electron microscopy revealed a combination of destructive and regenerative (compensatory-adaptive) processes in myocardium at the subcellular level. Muscle cell sarcolemma formed well-defined multiple "arches", protrusions, containing intracellular organelles (mitochondria) (Fig. 2a). Myocytes were often characterized by myofibril destruction, Z-line bend, and polymorphism

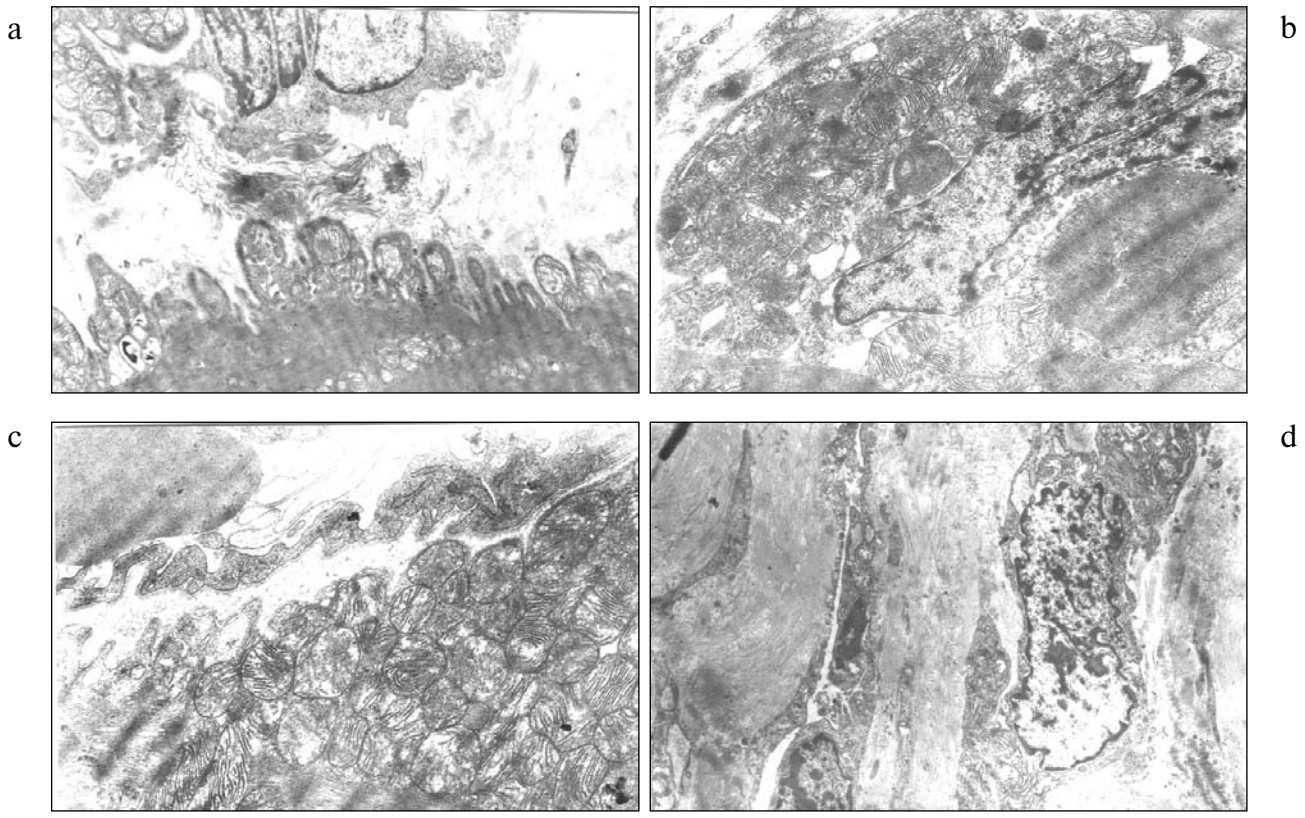

Fig. 2. Electron microscopy of postinfarct myocardium of rats treated with CoQ_{10} for 3 weeks before and 3 weeks after occlusion of coronary artery. a) Formation of cardiomyocyte sarcolemma arches; mitochondria inside these arches have damaged cristae; mitochondrial hyperplasia. Magnification ×7800. b) Atypical nucleus with deep invaginations of nuclear membranes and tightly adjacent mitochondria; polymorphism, hypertrophy, and destruction of mitochondria. Magnification ×13,200. c) Hypertrophy, hyperplasia, and destruction of mitochondria, sarcolemma, and myofibrils. The adjacent vascular wall has well-defined convolution of endothelium with well-developed granular cytoplasmic network. Vascular basal layer preserved. Magnification ×17,800. d) Scar formation: fibroblast cytoplasm mainly represents granular cytoplasmic network; major proportion of its small canals is extended up to formation of clefts and lacunas, which are opened into extracellular space; large accumulations of collagen fibrils around fibroblasts. Nucleus has scalloped shape. Magnification ×7800.

of myocyte nuclei. Nuclear membrane was either smooth (without protrusions and folds) or scalloped shape; in some cases, especially in myocardium of treated animals, nuclear membrane formed deep invaginations (folds) (Fig. 2b). This significantly increased nuclear surface area and therefore the contact square between nucleus and cytoplasm. Mitochondria were characterized by well-defined polymorphism: they had different shape, size, density of matrix, and positions of cristae. In hypertrophic myocardium, mitochondrial destruction related to their hyperfunction was characterized by crista destruction, loss of their parallel positioning and appearance of concentric, arched, and other shapes. However, mitochondrial destruction was compensated by hyperplasia and hypertrophy of these organelles. Mitochondrial hypertrophy and hyperplasia were more pronounced in CoQ_{10}-treated rats (Fig. 2c). Manifestations of vascular compensatory-adaptive reactions included the increase in the vascular lumen, and increase in sizes of endotheliocytes and their nuclei. These changes were more pronounced in rats treated with CoQ_{10}. Connective tissue appeared between destructive myocardiocytes, and this process was more pronounced in rats treated with CoQ_{10} (Fig. 2d).

Thus, the light microscopy morphological study showed earlier formation of scar tissue in rats treated with CoQ_{10}. Electron microscopy demonstrated similar compensatory-adaptive ultrastructural changes in the postinfarction myocardium of both groups of rats. However, in rats treated with CoQ_{10} there were more pronounced intracellular regeneration (characterized by the development of mitochondrial hypertrophy and hyperplasia) and active reaction of microvessels (increase in vascular lumen, increase in sizes of endotheliocytes and their nuclei).

DISCUSSION

Results of morphometric, morphological, and analytical studies have drawn a complex characteristic of postinfarction myocardium of rats. Chronic occlusion of coronary arteries was accompanied by formation of a necrotic focus and the development of compensatory hypertrophy of the LV myocardium. The postinfarction myocardium was characterized by destructive changes (breaks of myofibrils, disorganization of myofibrils, mitochondrial destruction, loss of cross-striation by cardiomyocytes, destruction of blood vessels) and also by the development of compensatory-adaptive processes such as cardiomyocyte destruction, mitochondrial hypertrophy and hyperplasia, reaction of microvessels, hypertrophy of stromal elements forming the scar tissue.

Myocardial infarction also caused significant decrease in antioxidants in the LV non-infarction myocardium: CoQ and α-tocopherol. Exhaustion of the antioxidant resources was typical only for hypertrophied LV myocardium; these changes were not observed in non-hypertrophied LV myocardium, where CoQ content remained unchanged. Previously we demonstrated that hypertrophied rat myocardium is characterized by more intensive generation of reactive oxygen species, particularly, hydroxyl radical [7, 16], and tissue level of hydroxyl radicals correlates with the degree of LV hypertrophy. Increased production of reactive oxygen species should inevitably result in exhaustion of antioxidant resources and the decrease in tissue resistance to oxidative stress. Indeed, after regional ischemia/reperfusion the necrotic zone was larger in hypertrophic rat myocardium than in normal myocardium [16].

Deficit of CoQ and α-tocopherol found in postinfarct myocardium suggests possible use of these compounds as putative cardioprotectors. It was reasonable to suggest that the cardioprotector effect of CoQ and vitamin E would be observed only in the case of significant increase in their tissue levels. In most studies administration of exogenous CoQ_{10} to experimental animals caused significant increase in its plasma ubiquinone concentrations [15, 17-19]. A more complicated problem is the evaluation of CoQ myocardial levels. There was a small increase in CoQ in myocardial homogenates [19] or selective increase of its mitochondrial level [15] or even complete lack of increase in CoQ myocardial level [17, 18, 20]. These changes may be attributed to use of different doses, modes and duration of CoQ_{10} administration as well as "type" of pharmaceutical dosage form of CoQ_{10} used. These factors are crucial for tissue bioavailability of this compound.

In this study, we used long-term per oral administration of CoQ_{10} to rats. This mode caused not only increase in plasma ubiquinone concentration [13] but also significant augmentation of myocardial CoQ content [12]. Evidently, plasma ubiquinone levels significantly vary depending on time passed after its administration. In our study, samples of blood plasma were taken during the second half of the inter-dose interval when ubiquinone concentrations were close to steady-state levels circulating in blood during most period of the day. These values were more than two orders of magnitude higher than CoQ_{10} concentrations observed in untreated postinfarction animals. Analysis of blood plasma samples taken 3-4 h after the per oral CoQ_{10} administration (the time interval of maximal concentrations) CoQ_{10} levels exceeded control values by more than 10-fold [13].

Coenzyme Q_9 is the dominating form of CoQ in rats. Tissue content of its decaisoprenoid homolog, CoQ_{10}, represents from 10 to 40% of total CoQ content in various tissues [11, 21]. The existence of specific functions and pathways for mutual introversions for these two homologs remain essentially unknown. Earlier studies on rats [19] and mice [15] have demonstrated an increase in CoQ_9 content after administration of CoQ_{10}. According to our data, long-term administration of CoQ_{10} is accompanied

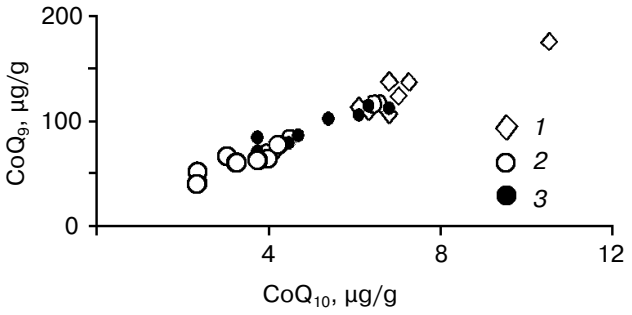

Fig. 3. Correlation between levels of CoQ_9 and CoQ_{10} in LV myocardium of three groups of rats ($r = 0.977$, $p < 0.001$): *1*) sham-operated rats; *2*) postinfarction untreated rats; *3*) postinfarction rats treated with CoQ_{10} for 3 weeks before and 3 weeks after occlusion of coronary artery.

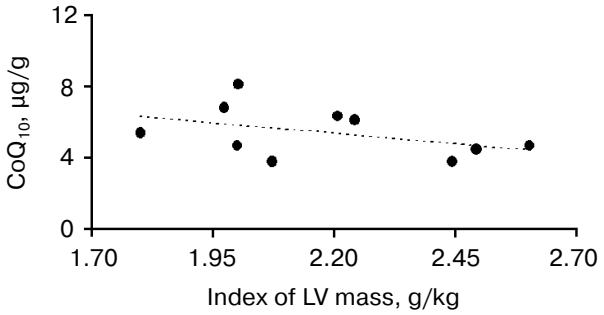

Fig. 4. Relationship between the LV hypertrophy degree and myocardial CoQ_{10} level ($r = -0.428$, $p > 0.05$) in the group of postinfarct rats treated with CoQ_{10} for 3 weeks before and 3 weeks after occlusion of coronary artery.

by the increased content of both homologs in the postinfarction myocardium. Interestingly, myocardial infarction had no influence on the ratio of CoQ_9 and CoQ_{10} concentrations (table). Moreover, augmentation of CoQ_9 content in myocardium of rats treated with exogenous CoQ was sufficient for maintenance of CoQ_9/CoQ_{10} ratio typical for myocardium. This fact together with existence of strong correlation between CoQ_9 and CoQ_{10} levels in myocardium of rats of all three groups (Fig. 3) suggest the existence of corresponding metabolic pathway for CoQ_{10} conversion.

Long-term administration of CoQ_{10} was accompanied by maintenance of higher levels of CoQ in the postinfarction myocardium. In untreated rats, the content of CoQ_{10} and CoQ_9 in the postinfarction myocardium was 43 and 45% less than in myocardium of sham-operated rats. In the treated animals, the content of CoQ_{10} and CoQ_9 in the postinfarction myocardium was just 25 and 23% less than in myocardium of sham-operated rats (table). It is possible that long-term administration of CoQ_{10} maintains increased levels of CoQ and provides increased myocardial resistance to subsequent ischemic oxidative stress. Replenishment of the antioxidant resources of myocardium caused significant reduction in the necrotic zone and the decrease in the mass index of postinfarction LV.

Maulik et al. already demonstrated ubiquinone efficiency in myocardial protection against oxidative stress [22]. Preventive administration of CoQ_{10} to mini pigs for 30 days improved LV functions and caused a 40%-reduction of the infarction zone after ischemia modeled in the perfused hearts *in situ*. Analysis of biopsy material obtained from the ischemia/reperfusion zone revealed higher CoQ_{10} levels in myocardium of CoQ_{10}-pretreated animals: in contrast to myocardium of control animals, ischemia/reperfusion did not cause a decrease in total CoQ_{10} content.

Administration of ubiquinone to rats for 6 weeks resulted in an increase in CoQ_{10} level and maintenance of antioxidant enzyme activities in myocardium [13]. This increased resistance of isolated hearts to damaging effect of perfusion with hydrogen peroxide solution. Crestanello et al. have shown [23] that pretreatment of rats with two administrations of CoQ_{10} increased its myocardial levels and improved recovery of functions of isolated hearts after ischemia/reperfusion.

Acute single dose administration of CoQ_{10} to rabbits (1 h before ischemia or during ischemia) or to rats (right after coronary artery occlusion) did not reduce the size of the infarction zone [24, 25].

In our study, only treated animals exhibited significant correlation between the size of the infarction zone and plasma CoQ concentrations: $r = -0.723$ ($p < 0.05$; CoQ_9) and $r = -0.839$ ($p < 0.01$; CoQ_{10}) (Fig. 1). In other words, the higher the plasma CoQ levels the lower the size of myocardial necrotic damage is. Since the increased plasma CoQ level is the source for replenishment of myocardial CoQ pool, it is relevant to suggest that higher levels of ubiquinone due to CoQ_{10} treatment provide its increased entry into myocardium.

It is clear that coenzymes Q represent only one link of the multi-component system responsible for compensatory processes in postinfarction myocardium. Utilization of CoQ under conditions of oxidative stress also depends on other elements of tissue antioxidant defense. Consequently, CoQ levels measured at the end of experiment may not necessarily be strictly proportional to the degree of myocardial damage, although a tendency for existence of such dependence has been recognized (Fig. 4). Unfortunately, we did not evaluate CoQ content in rat myocardium during the operation (for subsequent correlation with the size of infarction) because biopsy would be a serious damaging treatment. Nevertheless, the dependences found in this study provide enough experimental evidence that the increase in blood plasma and myocardial CoQ content caused by administration of exogenous ubiquinone may increase survival of myocardial cells under ischemic conditions. In rats treated with

CoQ_{10}, there was earlier and more intensive formation of scar tissue in myocardium; processes of intracellular regeneration were also more pronounced than in untreated rats. This resulted in reduction of the zone of necrosis and decrease in the index of LV mass.

Possible evaluation of effectiveness of CoQ_{10} in patients with LV hypertrophy, risk of the development of myocardial infarction, and heart failure requires subsequent clinical observations. In a recent publication, Rosenfeldt et al. [26] reported that in patients before heart operation, per oral administration of CoQ_{10} for two weeks resulted in its increase not only in plasma but also in myocardium (including mitochondria). Auricular trabeculae obtained from right atrium during heart operation were more resistant to hypoxia experiments *in vitro*. There are several reports [3, 27] that summarize long-term experience in the study and clinical application of CoQ_{10}; they recommend the use of CoQ_{10} in addition to traditional therapy of cardiovascular diseases.

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