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Single intravenous injection of CoQ_{10} reduces infarct size in a rat model of ischemia and reperfusion injury*

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ABSTRACT

Maintenance of mitochondrial activity and antioxidant features of coenzyme Q_{10} (CoQ_{10}) could be an effective background for treatment of acute myocardial ischemia. Dietary uptake of CoQ_{10} is limited to only a few percent. In urgent cases, parenteral administration of CoQ_{10} could provide fast increase of its plasma and myocardial levels. The aim was to evaluate whether a single intravenous (*i.v.*) injection of solubilized CoQ_{10} before ischemia/reperfusion (IR) could lead to replenishment of its myocardial levels and limits subsequent myocardial IR injury. Methods: 30 min prior to coronary artery occlusion rats received *i.v.* solubilized CoQ_{10} (30 mg/kg) or saline (1 ml/kg). After 30 min of ischemia and 120 min of reperfusion, infarct zone of left ventricle (LV) and quantity of CoQ_{10} in LV were determined. Cardiac rhythm was monitored through the whole experiment. Results: At the beginning of reperfusion, arrhythmias were recorded in 8 (from 9) in saline and 2 (from 9) in CoQ_{10}-treated rats. Arrhythmias in CoQ_{10}-treated rats arose later (40 ± 8 sec) and had less duration (26 ± 14 sec); 14 ± 13 sec and 52 ± 17 sec in saline treated rats respectively. At the end of reperfusion CoQ_{10} treated rats revealed: 2 fold higher CoQ_{10} content in LV ($p < 0.01$), limitation of infarct zone by 35% ($p < 0.01$). Higher levels of CoQ_{10} were accompanied by less infarct size ($r = -0.77$, $p < 0.001$). Conclusion: Single *i.v.* injection of CoQ_{10} effectively increased its myocardial levels and protected heart against IR injury by diminishing the size of the irreversibly damaged myocardium, decreasing frequency and duration of arrhythmias. The infarct zone inversely correlated with the quantity of CoQ_{10} in LV.

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Keywords: Coenzyme Q_{10}; Intravenous Injection; Myocardial Ischemia; Reperfusion Injury

1. INTRODUCTION

Myocardial infarct leads to irreversible loss of cardimyocytes accompanied by deterioration of contractile function and arrhythmias. Restoration of coronary blood flow limits necrosis of ischemic myocardium, but from the other hand reperfusion by itself results in myocardium damage [1]. Reperfusion initiates generation of free radicals, intracellular Ca^{2+}-overload, fast pH changes [2]. Excessive formation of free radicals results in cell death. Free radicals trigger inflammatory mediators such nuclear factor-kB sensitive to reduction/oxidative balance, interleukin-1b, tumor necrosis factor α [3,4]. It is well known that endogenous antioxidants such as glutathione peroxidase, superoxide dismutase and catalase are natural defense attenuating the ischemia/reperfusion (IR) injury [5]. Preservation of viable myocardium is possible with help of cardioprotectors.

Coenzyme Q_{10} (CoQ_{10}) is the endogenous compound, essential for mitochondrial function, possesses antioxidant and free radical scavenger features [6]. Long *per os* administration CoQ_{10} is recommended for prevention and treatment of coronary artery disease, arterial hypertension, heart failure, hyperlipidemia [7]. However, dietary uptake of CoQ_{10} is limited to only a few percent [8] and elevation of CoQ_{10} levels for cardioprotection requires long preventive treatment [9]. Replenishment of CoQ_{10} by cells could be effective during heart surgeries (preventive administration before procedures) or as inhibition of IR injury (restoration of coronary flow after myocardial infarction). Fast increase in plasma CoQ_{10} levels and subsequent uptake by myocardium could be reached with intravenous (*i.v.*) injection.

The aim of the study is to investigate the effects of single *i.v.* pretreatment of solubilized CoQ_{10} on its myo-

cardial level and IR injury.

2. METHODS

2.1. Animals

Animal-handling procedures followed the Guide for the Care and Use of Laboratory Animals [10] and with prior approval by the Bioethics committee of Lomonosov Moscow State University. Healthy male Wistar rats were housed separately in cages under a 12:12 hour light/dark cycle at 22˚C with free access to tap water and food.

2.2. Assessment of CoQ_{10} Levels in Myocardium 30 min after Its Single *I.V.* Injection

Anesthetized rats (sodium pentobarbital, 45 mg/kg, intraperitoneally) with venous catheters were used. Rats received *i.v.* a bolus of CoQ_{10} (30 mg/kg, solubilized CoQ_{10} in Kudesan solution, "Akvion", Russia)—"CoQ_{10}" group (n = 5) or saline (1 ml/kg, 0.9% NaCl)—"Control" group (n = 7). 30 min after injection rats were euthanized with 3 M KCl *i.v.*, left ventricle (LV) samples were collected, frozen and stored at −20˚C for further analysis. Quantitative analysis of myocardial CoQ_{10} levels was performed by reversed-phase HPLC with electrochemical detection as described previously [9].

2.3. Assessment of Cardioprotective Effects of Single *I.V.* Injection of CoQ_{10}

Surgical preparation. Rats anesthetized as described above were placed on a heated pad (body temperature 37.5˚C ± 0.5˚C). Continuous infusion of pentobarbitallum sodium as maintaining narcosis (20 mg/ml, 200 µl/h) was performed via plastic catheter in femoral vein ("KD Scientific 210", USA). To monitor blood pressure femoral artery catheter was connected to measurement equipment "Macintosh—MacLab" ("ADInstruments", Australia). Cardiac rhythm was monitored with a standard lead-1 electrocardiogram (ECG) ("MacLab", "ADInstruments", Australia).

Model of myocardial IR. After intubation (Inspira Advanced Safety Ventilator, Volume Controlled 55 - 7058, Harvard Apparatus) left thoracotomy with fourth rib removing was performed on the rat in supine position and the ligature with an atraumatic needle was placed around the left anterior descending coronary artery. Then a rat was allowed to recover for 30 min. A small plastic snare was threaded through the ligature and placed in contact with the heart. 30 min prior to occlusion rats received *i.v.* of 1 ml/kg 0.9% NaCl (group "Saline + IR", n = 11) or 30 mg/kg of solubilized CoQ_{10} (group "CoQ_{10} + IR", n = 10). The artery was occluded by applying tension to the ligature for 30 min and reperfusion was achieved by releasing the tension for 120 min. The sham-operated rats (group "Saline + Sham", n = 9) received saline bolus after thread placement and underwent the same study procedures except coronary artery occlusion.

Through each experiment blood pressure (BP) was measured as BPm = (BPs + 2xBPd)/3, where BPm—mean arterial blood pressure, BPs—systolic blood pressure, BPd—diastolic blood pressure.

Arrhythmia analysis was performed accordingly to Lambeth Conventions [11]: 1) number of rats with presence of any ventricle tachyarrhythmia (VTA); 2) number of VTA episodes per one rat; 3) time to development of the first VTA episode; 4) total duration of VRA episodes per one rat; 5) number of rats with lethal VTA.

Assessment of myocardial damage. At the end of reperfusion ligature around coronary artery was tighten again and Evans-Blue stain (5%, 0.5 ml) was infused *i.v.* to mark the risk zone (the non-stained tissue). Rats were euthanized with 3 M KCl *i.v.* Heart and liver were quickly removed. LV was separated, irrigated with cold water, frozen and stored at −20˚C for further analysis. To distinguish living myocardium within risk zone frozen LV was cut into 2 mm transverse slices, which were incubated in 2% triphenyl tetrazolium chloride (TTC) in pH 7.4 buffer at 37˚C for 15 min (**Figure 1**). On the slices the risk zone (ischemic area) was determined as ratio of not-stained with Evans-Blue myocardium to total myocardium area. The volume of infarct zone was calculated as ratio of not stained with TTC myocardium (necrotic tissue) to ischemic area.

Coenzyme Q_{10} assay in rat liver and LV was performed with HPLC [9]. LV myocardial level was estimated after assessment of myocardial damage.

2.4. Data Analysis

Values are presented as mean ± SD. Statistical analysis was performed with Statistica 8.0 (Stat Soft, Inc.). The differences in the means between the groups were tested using one-way ANOVA, followed by post hoc analysis for multiple comparisons (Student-Newman-Keuls method) to test for statistical significance ($p < 0.05$). Categorical values were compared using Fisher test ($p < 0.05$).

3. RESULTS

Single *i.v.* bolus of solubilized CoQ_{10} led in 30 min to enhanced myocardial levels by 18.5% ($p < 0.05$) versus control rats. 30 rats were used in experiments for assessment of single *i.v.* injection of CoQ_{10} for cardioprotection. 2 rats died in "Saline + IR" group and 1 rat in "CoQ_{10} + IR" group during ischemia.

Baseline values of blood pressure were similar in all experimental groups indicating equal initial conditions (**Figure 2**). Ischemia and reperfusion led to continuous

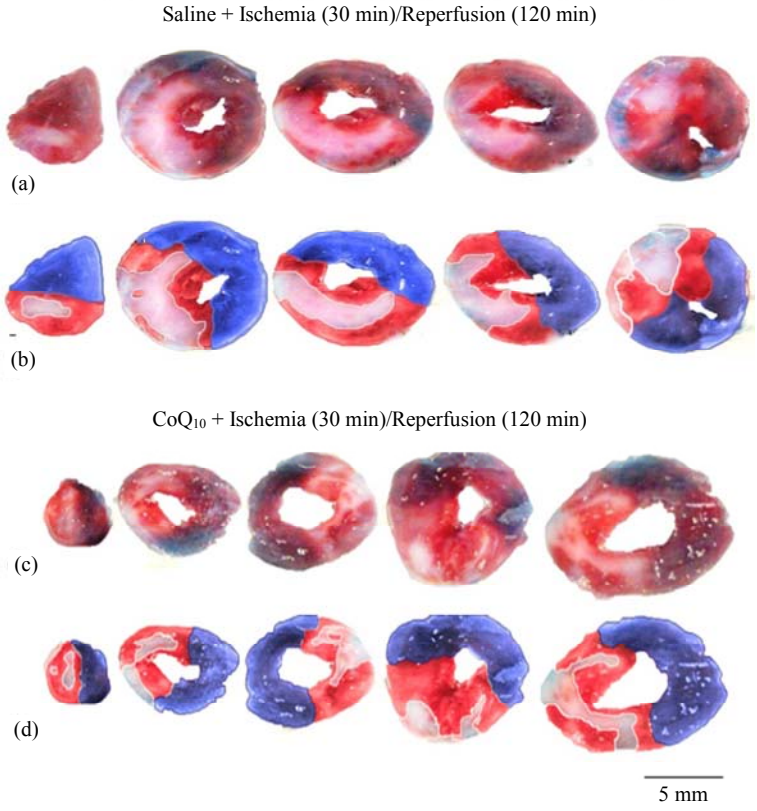

Figure 1. Slices of LV after 30 min of ischemia, caused by coronary artery occlusion, and subsequent 120 min of reperfusion, staining with Evans Blue and triphenyltetrazolium: infarct rats treated *i.v.* with saline (a) or CoQ_{10} (c). b and d—the same slices with differentiation of areas: blue stained area—not-ischemic myocardium, red stained area—ischemic not-infarcted myocardium, white stained area—necrose zone. *I.v.* injection of CoQ_{10} (30 mg/kg) 30 min prior to coronary occlusion resulted in limitation of portion of irreversibly damaged myocardium.

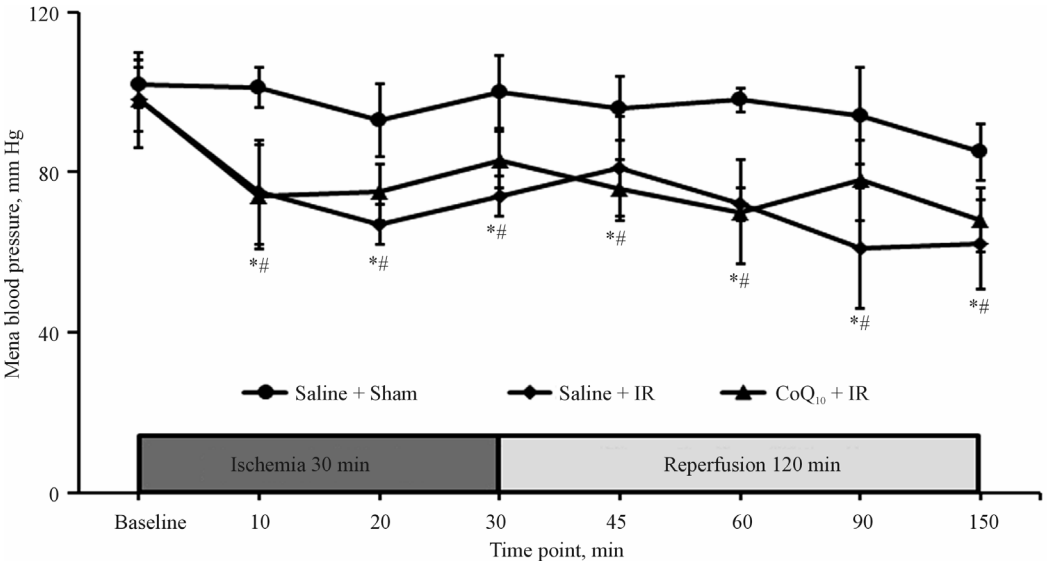

Figure 2. Values of mean blood pressure measured in femoral artery of sham-operated (Saline + Sham) and CoQ_{10} (CoQ_{10} + IR) or saline (Saline + IR) treated infarct rats. $^{*}p < 0.05$ vs baseline, $^{\#}p < 0.05$ vs sham-operated rats.

decrease of BPm. CoQ_{10}-treated rats had the same profile of BPm curve as saline treated infarct rats. Sham-operated rats had slight decrease of BPm during the whole experiment, but without statistical significance within group, which possibly could be related with continuous infusion of anesthetic.

During ischemia 10 rats of 11 in group "Saline + IR" had episodes of arrhythmias. Pretreatment with CoQ_{10} had no impact on arrhythmias characteristics during ischemia (**Table 1**). However, at the beginning of reperfusion arrhythmias occurred in 8 of 9 animals in the "Saline + IR" and in 2 of 9 animals in "CoQ_{10} + IR". In "CoQ_{10} + IR" group reperfusion arrhythmias appeared later and had shorter duration (**Table 1**).

At the end of reperfusion infarct size of saline treated infarct rats was 47% ± 6%. Single *i.v.* CoQ_{10} injection prior to coronary occlusion limited irreversible myocardial cell injury to 31 ± 7%. These groups had no statistical significance in the volume of area at risk that pointed to equal baseline ischemia conditions (**Figures 1** and **3**).

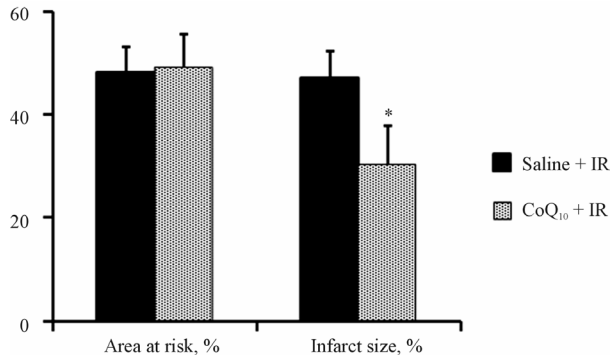

Figure 3. Myocardial infarct size quantification presented as the percentage of the area at risk. Assessment was performed after pre-treatment with *i.v.* injection of CoQ_{10} ("CoQ + IR") or saline ("Saline + IR") 30 min prior to a regional myocardial ischemia (30 min) and reperfusion (120 min). *I.v.* injection of CoQ_{10} prior to coronary occlusion resulted in reduced portion of irreversibly damaged myocardium by 35% in comparison with saline-treated rats ($p < 0.01$).

I.v. injection of CoQ_{10} led to enhance levels of CoQ_{10} in myocardium and liver: 180 min after administration of CoQ_{10} its level was increased in LV by 210% ($p < 0.01$), in liver by 2081% ($p < 0.01$) in comparison with sham-operated rats (**Figure 4**). There was no difference in CoQ_{10} tissue levels between saline-treated infarct rats and sham-operated rats. The relationship between infarct size and myocardial content of CoQ_{10} in LV of both infarct groups was revealed: the higher levels of CoQ_{10} were accompanied by less quantity of damaged myocardium ($r = -0,77$, $p < 0.001$; **Figure 5**).

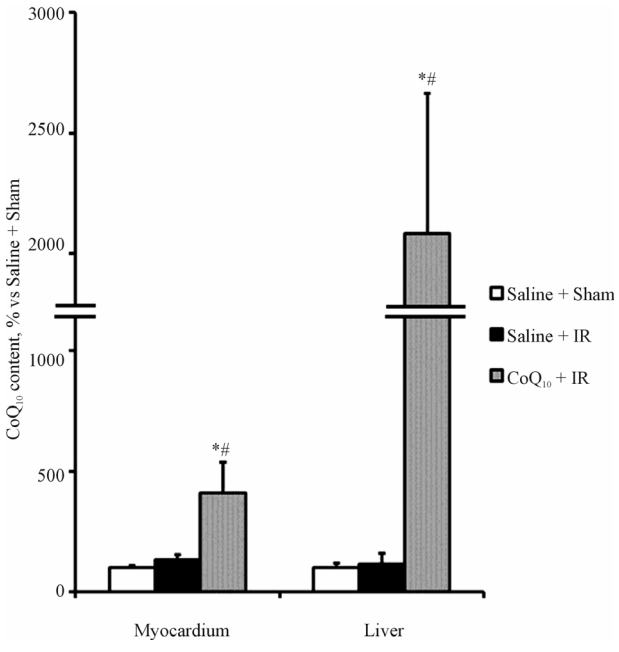

Figure 4. Myocardial and liver CoQ_{10} levels measured 180 min after single *i.v.* injection of CoQ_{10} (CoQ_{10} + IR) or saline (Saline + IR) and following ischemia-reperfusion (IR) relatively to sham-operated animals (Saline + Sham). Increased content of CoQ_{10} after its single *i.v.* injection 30 min prior to coronary artery occlusion were observed in LV and liver. $^{*}p < 0.05$ vs "Saline + Sham", $^{\#}p < 0.05$ vs "Saline + IR". Percentages were calculated relatively to sham-operated animals.

Table 1. Cardiac rhythm alterations in rats underwent myocardial ischemia/reperfusion.

	Ischemia		Reperfusion	
	Saline + IR	CoQ_{10} + IR	Saline + IR	CoQ_{10} + IR
Rats used, n	11	10	9	9
Rats with lethal VTA* (n)	2	1	0	0
Rats with presence of any VTA (n)	8	8	8	2
Number of VTA episodes per one rat	6.7 ± 1.4	6.5 ± 2.2	5.1 ± 1.7	6.5 ± 3.5
Time to development of the first VTA episode from the start of ischemia or reperfusion, sec	364 ± 55	374 ± 62	14 ± 13	40 ± 8
Total duration of VTA episodes per one rat, sec	103 ± 41	92 ± 58	52 ± 17	26 ± 14

*VTA—ventricle tachyarrhythmia.

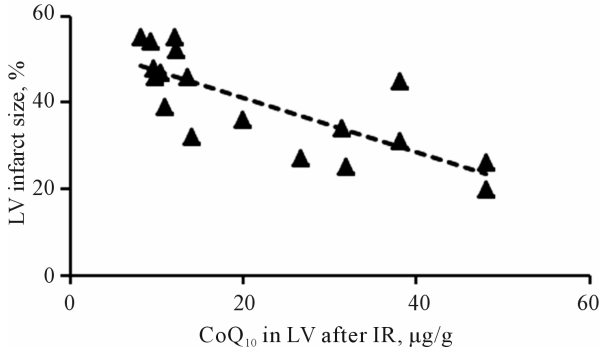

Figure 5. Correlation between CoQ_{10} levels in LV of infarct rats and LV infarct size ($r = -0.77$, $p < 0.0001$) was calculated. CoQ_{10} or saline was injected 30 min prior to coronary artery occlusion and following regional myocardial ischemia (30 min) and reperfusion (120 min).

4. DISCUSSION

The most effective way to limit the portion of irreversibly damaged cardiomyocytes is rapid and complete restoration of coronary blood flow. However, reperfusion itself contributes to myocardial injury. The presented results demonstrated that single *i.v.* injection of CoQ_{10} resulted in replenishment of its levels in myocardium, which was accompanied by limitation of IR injury.

Tissue preservation can be achieved if the restoration of blood flow is accompanied by additional treatment as it is presented in our study by preventive *i.v.* administration of CoQ_{10}.

Previously, on the rat model of MI induced by coronary artery ligation, it was shown the limitation of infarct size by 40% and limitation of myocardial hypertrophy as a result of long preventive (3 weeks) and post-infarct (3 weeks) *per os* administration of CoQ_{10}. In that study, treatment of CoQ_{10} during 6 weeks led to elevation of its myocardial levels by 20% - 30%. [9] In the present study single *i.v.* CoQ_{10} injection resulted in a similar increase of its levels in myocardium 30 min after administration. Therefore, this time was chosen for CoQ_{10} injection on the model of myocardial IR.

Free radicals are generated in postischemic myocardium and when exceeding the ability of the cellular native free radical scavenging features it lead to cardiomyocytes dysfunction and death. CoQ_{10} protects myocardium from IR injury due to bioenergetics and antioxidant properties [6]. CoQ_{10} neutralizes the excessive formation of reactive oxygen species by suppression of NADPH oxidase expression [12]; scavenges lipid peroxides [13]; prevents nitrative stress by inhibition of excess NO production [14]. Inhibition of opening mitochondrial permeability transition pore, induced by reactive oxygen species, is one of the possible mechanisms of cardioprotective effect of CoQ_{10} [15-18]. Protective mechanism of CoQ_{10} can be associated with multiple anti-inflammatory effects by influencing the expression of NFkB1-dependent genes [19] and non-specific restoration of damaged membranes [20].

CoQ_{10} is recommended for long-term adjunctive therapy for various cardiovascular disorders, as hypotensive and cardioprotective agent [21]. Correlation between tissue levels of CoQ_{10} and severity of cardiovascular pathology is found in man [7,21-23]. Low levels of CoQ_{10} are observed in 70% - 75% of patients with heart disease and strong correlation is estimated between reduced levels of CoQ_{10} and mortality in patients with congestive heart failure [24].

However, CoQ_{10} bioavailability after *per os* administration is extremely low [8]. In urgent cases, it is necessary to increase myocardial CoQ_{10} content rapidly, which could be reached via *i.v.* injection. Few experimental studies explored that intracoronary or *i.v.* administration of CoQ_{10}-loaded liposomes increased its myocardial levels, limited zone of IR injury and maintained heart function [20,25-27]. Cardioprotective effects of *i.v.* CoQ_{10}-loaded liposomes administration before ischemia/reperfusion were evaluated mostly on isolated hearts [25-27] and a few *in vivo* studies were conducted [20]. In that studies it was shown that CoQ_{10} administration improved recovery of function (diastolic pressure), aerobic efficiency and creatine kinase activity after reperfusion [26]; protected endothelial-dependent and endothelial-independent vasodilation after IR [25]; improved recovery of diastolic pressure and mytochondrial function at the end of IR [27]; limited infarct size [20].

In our *in vivo* study, it was shown at the first time that *i.v.* injection of solubilized CoQ_{10} protected myocardium against subsequent IR as effective as liposome forms. *I.v.* injection of solubilized CoQ_{10} provided quickly elevation of its plasma levels and tissue uptake. Liver had a high capacity to uptake CoQ_{10} and could contribute significantly to maintenance of plasma and myocardial CoQ_{10} concentrations for a long period. CoQ_{10} myocardial levels inversely correlated to the infarct size. Antiarrhythmic effect of CoQ_{10} revealed in the present study was also reported in previous studies [21,28].

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