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Cardioprotection with Intravenous Injection of Coenzyme Q10 is limited by Time of Administration after Onset of Myocardial Infarction in Rats

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Abstract

Objective: Coenzyme Q_{10} (CoQ_{10}) levels are decreased in patients with cardiovascular diseases. The bioavailability of orally ingested CoQ_{10} is limited to 2–3%, and long-term administration is required to increase the level of CoQ_{10} in myocardium for cardioprotection. Intravenous (IV) administration of solubilized CoQ_{10} immediately after coronary occlusion has been shown to increase myocardial levels rapidly and to protect against cardiac ischemia. The aim of this study was to determine the length of time following onset of myocardial infarction (MI) for which a single IV administration of CoQ_{10} was cardioprotective.

Methods: A single IV injection of solubilized CoQ_{10} (30 mg/kg, 1 ml/kg) or saline (1 ml/kg) was administered at either minute 60 or minute 180 after the onset of MI induced by coronary artery ligation in rats.

Results: Twenty-one days after injection, CoQ_{10} levels were still high in both the 60 and 180 minute groups. Rats treated with CoQ_{10} 60 min after ligation had a significantly larger mass of viable left ventricle (LV) myocardium, limited LV dilatation, and improved cardiac contractile and relaxation capacity compared with controls. CoQ_{10} levels were significantly correlated with LV end-systolic volume (r=-0.65), end-diastolic volume (r=-0.56), ejection fraction (r-=0.67), and LV relaxation (r=-0.64) (p<0.001). IV administration of CoQ_{10} 180 min after occlusion prevented signs of right ventricle hypertrophy but did not limit LV damage.

Conclusion: A single IV injection of solubilized CoQ_{10} (30 mg/kg) at minute 60 effectively limited LV damage and deterioration of function after coronary ligation in rats; however, the same protective effects were not seen with CoQ_{10} injection administered at minute 180.

Background

Coenzyme Q_{10} (CoQ_{10}, also known as ubiquinone) is a lipid-soluble antioxidant synthesized endogenously [1]. Its plasma levels are lower in patients more predisposed to cardiovascular disorders [2]. Previous studies have shown decreased levels of CoQ_{10} in cardiac patients and a positive correlation of plasma CoQ_{10} levels with overall survival [3-7]. The bioavailability of CoQ_{10} administered orally is very low (2–3%) [8]. Levels increase slowly during the 1-2 hours after oral administration, with maximum plasma concentration by 6-8 hours [9]. For cardioprotection, CoQ_{10} should be taken over a long period of time to increase myocardial levels [10]. A number of studies estimating the cardioprotective efficacy of parenteral administration of CoQ_{10} for preventive use of CoQ_{10}-loaded liposomes in ischemic-reperfusion injury model either *in vitro* or with intracoronary injection have been performed [11-12]. In major cardiovascular events, such as Myocardial Infarction (MI), urgent cardioprotection is crucial after the onset of ischemia and can be achieved with a fast increase in myocardial CoQ_{10} levels after intravenous (IV) CoQ_{10} injection. We previously demonstrated that IV injection of CoQ_{10} immediately after coronary occlusion increased myocardial CoQ_{10} levels rapidly and limited Left Ventricle (LV) myocardial damage and deterioration of function [13].

The aim of this study was to determine the length of time following onset of MI for which a single IV administration of CoQ_{10} was cardioprotective.

Methods

Animals

Eighty 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. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals and with the prior approval of the bioethics committee of Lomonosov Moscow State University [14].

Study design

The study included two separate series of experiments designed to reveal whether solubilized CoQ_{10} had cardioprotective efficacy if injected once IV at minute 60 or minute 180 after coronary artery occlusion. Effects of CoQ_{10} treatment assessed on day 21 after MI onset included size of infarct zone; Right Ventricle (RV) and LV hypertrophy;

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concentration of CoQ_{10} in plasma, LV, myocardium, and liver; and cardiac function.

MI model

The rats were anesthetized with sodium pentobarbital 20 mg/mL solution intraperitoneal injection (45 mg/kg) and placed on a heated surgical pad at constant body temperature 37 ± 0.5 °C. Under aseptic conditions, a plastic catheter was inserted into a femoral vein for drug injection. Rats were endotracheally intubated and connected to a rodent ventilator (Inspira Advanced Safety Ventilator, Volume Controlled 55-7058; Harvard Apparatus, Holliston, MA, USA) with stroke volume and respiratory rate calculated automatically on the basis of animal weight. Left thoracotomy with removal of the 4th rib was performed with the rat in supine position, and the Left Anterior Descending Coronary Artery (LAD) was occluded with an atraumatic needle and 6-0 Prolene® suture (Ethicon Endo-Surgery Inc., Blue Ash, OH, USA). Some rats underwent a sham procedure, which included suture placement around the LAD without tying it. Blanching of the wall of the LV indicated a lack of perfusion. The chest cavity was closed in layers. The rats were weaned off the ventilator and the endotracheal tube was removed after spontaneous resumption of respiration.

Drug injection after MI modeling

A bolus injection of 30 mg/kg solubilized CoQ_{10} (30 mg/mL Kudesan solution; JSC Akvion, Moscow, Russia) or saline (0.9% NaCl, 1 mL/kg) was administered into a femoral vein at either minute 60 or minute 180 after coronary artery occlusion. The sham-operated rats received 0.9% NaCl 1 mL/kg (Table 1). All rats also received gentamicin 4 mg/kg intraperitoneally immediately following surgery and twice a day at 8 am and 8 pm during the subsequent 3 days to prevent infection.

Measurement of LV function

LV pressure-volume values were assessed with a 1.4-Fr conductance catheter (SPR-839; Millar Instruments Inc., Houston, TX, USA) inserted into the LV through the right common carotid artery of anesthetized rats under closed-chest conditions. The animal was stabilized for 10 min, and baseline values during steady-state were recorded at a 1,000-Hz sampling rate (Pressure Volume Conductance System, Millar Instruments) and analyzed using PVAN version 3.4 software (Millar Instruments). The raw conductance volumes were corrected for parallel conductance using a hypertonic saline IV bolus (10 μl, 15% saline). Based on the pressure-volume loops obtained, the following parameters were calculated: Heart Rate (HR), end-systolic pressure, End-Diastolic Pressure (EDP), End-Systolic Volume (ESV), End-Diastolic Volume (EDV), Stroke Volume (SV), Cardiac Output (CO), arterial elastance, a measure of ventricular afterload (Ea), Ejection Fraction (EF), contractility as +dP/dt max (peak rate of pressure rise), and relaxation as −dP/dt max (peak rate of pressure decline).

Blood samples were drawn using an arterial catheter after assessment of LV function, and rats were sacrificed using 3M KCl IV. Samples of liver and heart were collected. LV and RV were separated, irrigated with cold water and weighed. Samples were frozen and stored at -20°C for further analysis.

Myocardial hypertrophy and infarct size

LV and RV hypertrophy was calculated based on an accepted method of hypertrophy assessment, ratio of affected organ weight to body weight [15-17]. Triphenyltetrazolium (TTC) staining was used to determine myocardial infarct size [18]. The frozen LV was transversely sectioned and slices were incubated in TTC (2%, solution in phosphate buffer, pH=7.4) for 10 min at 37°C. The infarct zone of post-MI myocardium on day 21 was characterized by either multifocal intramural MI (mostly the 60-min group) or by aneurisms (saline-treated infarct rats) (Figure 1). In rats with aneurisms, infarct length was calculated as ratio of total length of the scar outer surface to slice circumference. Because there were different types of MI, numerical analysis of the infarct zone (infarct length vs. infarct area) was impossible and calculation of infarct area was not useful for comparison. Descriptive comparison of damaged myocardium between groups (intramural necrosis vs. aneurism) was performed.

Measurement of tissue CoQ_{10} levels

CoQ_{10} assay in plasma, myocardium, and liver was performed by reversed-phase High-Performance Liquid Chromatography (HPLC) with electrochemical detection. Immediately after collection, blood samples were centrifuged at 3,000 rpm for 10 min and the plasma transferred into an Eppendorf polypropylene tube, frozen, and stored at -20 °C. After thawing at room temperature, 100 μL of the sample was transferred to a separate Eppendorf tube for further extraction. Myocardium and liver samples were homogenized in distilled water (1:4 w/v) using an ultrasound homogenizer (Sonoplus mini20; Bandelin Electronic GmbH & Co. KG, Berlin, Germany), and the obtained homogenates were used for extraction of CoQ_{10}.

Ethanol (200 μL) and n-hexane (500 μL) were added to 100 μL of plasma or tissue homogenate and shaken thoroughly for 10 min. The mixture was then centrifuged for 3 min at 3,000 rpm. The n-hexane upper layer was collected, and 500 μL of n-hexane was added to the remaining portion of the sample. The extraction procedure was repeated again. Pooled extract was completely evaporated, then dissolved in 100 μL of ethanol. The oxidized form of CoQ_{10} in extracts

Series	Groups	n, underwent surgery	n, used for analysis	m_0	m_{21} *	p m_0 vs m_{21}	LV$_{ind}$	RV$_{ind}$
60 min	**MI+Saline**		9	396 ± 49	450 ± 49	<0.05	1.95 ± 0.13*	0.56 ± 0.08*
	MI+CoQ₁₀	48	12	404 ± 38	455 ± 36	<0.05	2.07 ± 0.17*	0.52 ± 0.13*
	Sham+Saline		10	386 ± 35	448 ± 35	<0.05	1.8 ± 0.13	0.46 ± 0.08
180 min	**MI+Saline**		9	330 ± 33	368 ± 38	<0.05	2.26 ± 0.24*	0.62 ± 0.12*
	MI+CoQ₁₀	32	8	323 ± 16	362 ± 19	<0.05	2.28 ± 0.17*	0.55 ± 009†
	Sham+Saline		7	324 ± 31	364 ± 34	<0.05	2.09 ± 0.12	0.50 ± 0.04

* LV$_{ind}$, LV index of hypertrophy (LV weight/rat weight); m_0, rat mass at the start of experiment; m_{21}, rat mass on day 21; RV$_{ind}$, RV index of hypertrophy (RV weight/rat weight). In each series there was no difference in body weight between groups on day 1 of the experiment; 21 days after surgery, rat weights were higher than initially, but without statistical significance between groups.
*p < 0.05 vs. sham+Saline
†p < 0.05 vs. MI+saline
Statistical differences should be considered only between groups within separate 60-min or 180-min series.

Table 1: Experimental groups of rats for CoQ_{10} cardioprotective efficacy evaluation on the MI model.

was reduced carefully and completely by adding aliquots of sodium tetrahydroborate solution in ethanol and confirmed by HPLC. An aliquot of reduced extract was analyzed with reversed-phase HPLC using a model 580 pump and Coulochem III electrochemical detector (Environmental Sciences Associates Inc., San Francisco, CA, USA) and HPLC column (Luna® 5 μm C18[2] 100 Å LC Column, 150 × 4.6 mm; Phenomenex®, Torrance, CA, USA). Electrochemical detection was carried out using analytical cell model 5011 (Environmental Sciences Associates Inc.) with voltage settings of −50 and +350 mV at the first and second potentiostats. The mobile phase contained 0.3% NaCl in an ethanol-methanol-7% $HClO_4$ mixture (975:15:10 v:v:v) at a flow rate 1.4 mL/min. Retention time for CoQ_{10} was 10 min. Environmental Sciences Associates Inc. software was used for registration and analysis of chromatographic data.

Statistical analysis and data presentation

Values are presented as mean ± standard deviation. Statistical analysis was performed with Statistica 8.0 (Stat Soft Inc., Tulsa, OK, USA). The differences in the means between groups within each separate series were tested using one-way analysis of variance, 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's exact test ($p<0.05$).

Results

Effects of CoQ_{10} injected at minute 60

Forty-eight rats underwent MI modeling with coronary artery occlusion or Sham procedure. Seventeen rats died during the first day (35%), and 31 rats were used for analysis on postoperative day 21. There were no differences in body weight between groups on day 1 of the experiment. On postoperative day 21, body weights were higher than at baseline but not significantly different between groups (Table 1).

LV Function

LV function was assessed under closed-chest conditions on postoperative day 21, prior to analysis of myocardial damage and hypertrophy (Table 2). MI resulted in significant deterioration of LV function, as evidenced by decreased systolic and diastolic indices. The increased pressure, systolic and diastolic end volumes and decreased SV, EF, CO, +dP/dtmax, and −dP/dtmax were recorded in saline-treated MI animals compared with sham-operated animals, which reflected dilatation of the LV chamber and impaired cardiac contractile and relaxation capacity.

A minor decline in cardiac dysfunction was observed in CoQ_{10}-treated infarct animals compared with saline-treated infarct animals. In infarct rats receiving a single IV injection of CoQ_{10}, LV end-systolic and end-diastolic volumes were significantly lower than those of MI+saline groups, indicating that CoQ_{10} limited chamber dilatation after MI. There was no difference in SV, CO, or +dP/dtmax between sham-operated and CoQ_{10}-treated rats. EF and −dP/dtmax were significantly improved compared with MI+saline groups. EDP increased significantly in saline-treated infarct animals, but not in animals treated with CoQ_{10}. Increased EDP values in saline-treated infarct rats indicate the onset of diastolic dysfunction, which was limited in the CoQ_{10}-treated group. Ea, an index of afterload, was elevated in saline-treated MI but not in CoQ_{10}-treated rats compared with sham-operated rats. There were no significant differences in HR among all groups.

Myocardial damage and hypertrophy

Infarct length was calculated as ratio of the length of scar outer surface to slice circumference. In the saline-treated group, five of nine animals had connective tissue scars of 35.6 ± 5.1% and four of nine had a mix of myocardium and connective tissue within LV walls. All 12 CoQ_{10}-treated animals had scars localized within ischemic LV walls without complete replacement of myocardium with connective tissue, a significant difference compared with MI+Saline animals (Figure 2). Different types of MI made numerical analysis of the infarct zone (infarct length vs. infarct area) impossible. MI resulted in compensatory hypertrophy of the LV and RV (Table 1).

CoQ_{10} content

To test whether improved cardiac function and limitation of LV damage was related to CoQ_{10} levels, the content of CoQ_{10} in plasma, myocardium, and liver was measured (Figure 3A). CoQ_{10} level was observed to be significantly increased in plasma, LV, and liver in CoQ_{10}-treated MI rats compared with saline-treated MI and sham-operated

Parameter	Sham+Saline	MI+Saline	MI+CoQ$_{10}$
HR, bpm	395.9 ± 43.7	368.7 ± 38.2	357.9 ± 28.2
ESV, μl	86.2 ± 4.2	158.1 ± 6.5*	109.8 ± 26.6*†
EDV, μl	189 ± 9.2	282.7 ± 8.2*	224.8 ± 67.3*†
ESP, mmHg	132.1 ± 6.8	135.2 ± 6	141.2 ± 17.4
EDP, mmHg	8.4 ± 1.5	13.1 ± 2.2*	7.7 ± 1.1†
SV, μl	86.1 ± 5.6	54.7 ± 11.1*	76.3 ± 13.3†
EF, %	52.2 ± 3.1	17.0 ± 8.0*	37.1 ± 3.7*†
CO, ml/min	41.9 ± 3.8	21.7 ± 7*	33.5 ± 6†
Ea, mmHg/μL	3.3 ± 2	5.9 ± 0.6*	4.1 ± 0.4†
+dP/dt max, mmHg/s	9843.4 ± 580	7264.5 ± 1851.6*	8685.9 ± 1549.5†
-dP/dt max, mmHg/s	10661,3 ± 1410,8	5975,4 ± 561,6	7738,1 ± 1232

Values are expressed as mean ± standard deviation. CO, cardiac output; +dP/dt$_{max}$, maximum first derivative of change in pressure rise with respect to time; -dP/dt$_{max}$, maximum first derivative of change in pressure fall with respect to time; Ea, arterial elastance; EDP, end-diastolic pressure; EDV, end-diastolic volume; EF, ejection fraction; ESP, end-systolic pressure; ESV, end-systolic volume; HR, heart rate; MI, myocardial infarct; SV, stroke volume.
*$p < 0.05$ vs. sham+saline
†$p < 0.05$ vs. MI+saline

Table 2: Parameters of cardiac function in rats on the day 21 after coronary occlusion with and without CoQ_{10} injection at minute 60 after coronary artery occlusion.
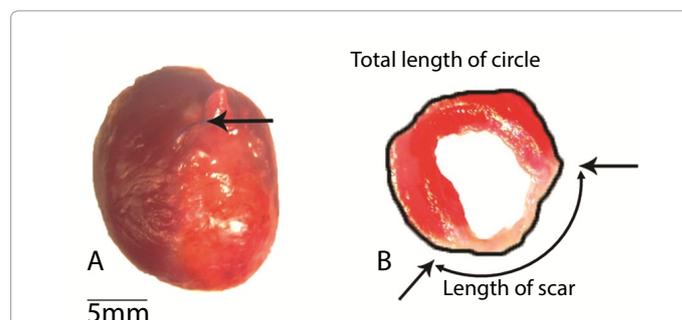
Figure 1: Images of the LV on the 21st day after LAD occlusion. Panel A: Arrow showing point of ligature. MI hearts revealed irreversible loss of myocardial tissue, and scar formation completely replaced myocardium within the LAD supply region. Panel B: Transverse slice of LV stained with triphenyltetrazolium chloride showing transmural infarction with pronounced wall thinning and aneurysm formation. Percentage of infarcted myocardium calculated as ratio of scar length to total circumference. LAD: Left anterior descending coronary artery; LV: Left ventricle; MI: Myocardial infarction.
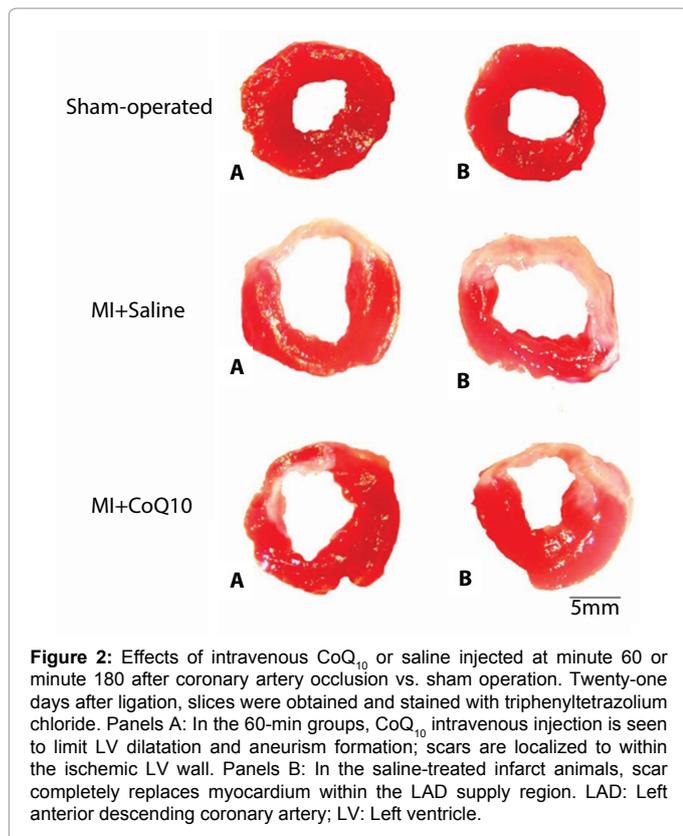
Figure 2: Effects of intravenous CoQ_{10} or saline injected at minute 60 or minute 180 after coronary artery occlusion vs. sham operation. Twenty-one days after ligation, slices were obtained and stained with triphenyltetrazolium chloride. Panels A: In the 60-min groups, CoQ_{10} intravenous injection is seen to limit LV dilatation and aneurism formation; scars are localized to within the ischemic LV wall. Panels B: In the saline-treated infarct animals, scar completely replaces myocardium within the LAD supply region. LAD: Left anterior descending coronary artery; LV: Left ventricle.

rats; values were calculated relative to sham-operated animals. There was no difference in tissue levels of CoQ_{10} between saline-treated MI and sham-operated rats.

Significant correlations were found between the content of myocardial CoQ_{10} and ESV (r= −0.65, $p < 0.001$), EDV (r=−0.56, $p<0.001$), EF (r=0.67, $p<0.001$), and -dp/dt max (r =−0.64, $p<0.001$), demonstrating the relationship between LV function and CoQ_{10} levels in the LV of infarct rats (Figure 3B).

Effects of CoQ_{10} injected at minute 180

Thirty-two rats underwent an MI-inducing surgical procedure or Sham procedure. Eight rats died during the first day (25%) and 24 rats were used for analysis on postoperative day 21. There were no differences in body weight between groups on the first day of the experiment; body weight was higher 21 days after surgery than it was initially, but was not significantly different between groups (Table 1).

Myocardial damage

Infarcted saline-treated animals had LV aneurisms, with infarct length 38.1 ± 6.0% of total LV circumference. CoQ_{10} injected 180 min after onset of MI did not limit myocardial loss or aneurism formation (infarct length 36.5 ± 6.8% of total LV circumference). RV hypertrophy was observed only in saline-treated infarct animals (Table 1).

LV function

LV function was assessed under closed-chest conditions on postoperative day 21, prior to analysis of myocardial damage and hypertrophy. MI resulted in significant deterioration of LV function of saline treated rats. CoQ_{10} injection performed 180 min after occlusion had no efficacy for protection of cardiac function.

CoQ_{10} content

Significant increases in CoQ_{10} levels 21 days after a single IV injection were observed in plasma (by 78%, $p < 0.01$), LV (by 90%, $p<0.05$), and liver (by 1665%, $p < 0.001$) of CoQ_{10}-treated MI rats; values were calculated relative to sham-operated animals. There were no differences in CoQ_{10} levels in plasma, LV, or liver between saline-treated MI and sham-operated rats.

Discussion

The ligation of the coronary artery caused severe damage to the myocardium, as illustrated by pronounced wall thinning, aneurysm formation and compensatory hypertrophy: LV and RV myocardium underwent heart remodeling similar to that in saline-treated infarct rats (Figure 2). The loss of myocardial tissue caused severe heart failure, characterized by dilatation of the LV chamber; increased end-systolic and diastolic volumes, EDP, and LV relaxation time; and reduced CO and EF, indicating the progression of systolic and diastolic dysfunction (Table 2).

We previously assessed IV injection of solubilized CoQ_{10} (30 mg/kg) immediately (10 min) after coronary artery ligation [13]. In that study, CoQ_{10} injection led to a rapid increase in myocardial levels of CoQ_{10} in healthy rats by approximately 20%, measured 30 min after administration. That elevation in myocardial CoQ_{10} was sufficient for cardioprotection in a model of irreversible coronary occlusion in rats receiving IV injection of CoQ_{10} 10 min after occlusion. There were undefined time periods in which a rapid increase in CoQ_{10} level following a single IV injection of solubilized CoQ_{10} could protect the heart after the onset of MI. In the present study, a single IV injection of solubilized CoQ_{10} (30 mg/kg) at minute 60 after coronary ligation, but
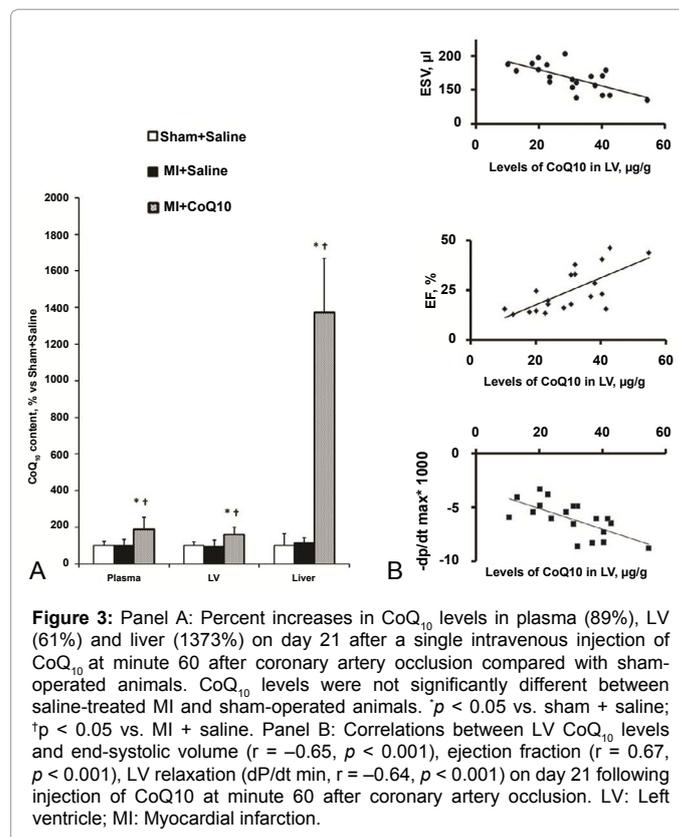
Figure 3: Panel A: Percent increases in CoQ_{10} levels in plasma (89%), LV (61%) and liver (1373%) on day 21 after a single intravenous injection of CoQ_{10} at minute 60 after coronary artery occlusion compared with sham-operated animals. CoQ_{10} levels were not significantly different between saline-treated MI and sham-operated animals. $^*p < 0.05$ vs. sham + saline; $^†p < 0.05$ vs. MI + saline. Panel B: Correlations between LV CoQ_{10} levels and end-systolic volume (r = −0.65, $p < 0.001$), ejection fraction (r = 0.67, $p < 0.001$), LV relaxation (dP/dt min, r = −0.64, $p < 0.001$) on day 21 following injection of CoQ10 at minute 60 after coronary artery occlusion. LV: Left ventricle; MI: Myocardial infarction.

not at minute 180, was shown to be effective in limiting LV myocardial damage and deterioration of function.

The CoQ_{10} dose used in our study was comparable to the doses used by others reporting the cardioprotective effects of acute preventive CoQ_{10} administration *in vitro* (5-15 mg/kg) [11,12,19,20]. Previously we demonstrated in a rat model of MI *in vivo* the effect of irreversible coronary artery occlusion on myocardial CoQ_{10} content and limitation of LV remodeling with long-term CoQ_{10} (10 mg/kg/day) pretreatment [10]. In that study, the CoQ_{10} content of the hypertrophied myocardium of saline-treated infarct animals decreased. Oral administration of CoQ_{10} for 3 weeks before and 3 weeks after coronary occlusion maintained increased levels of CoQ_{10} in myocardium (by 31% vs. untreated infarct rats) and plasma, resulting in a smaller infarct size and less LV hypertrophy. A correlation of CoQ_{10} in plasma vs. infarct size (r=−0.839, $p < 0.01$) was found for CoQ_{10}-treated rats. Recently it was reported that single preventive IV injection of CoQ_{10} (30 mg/kg) increased its myocardial levels and resulted in a smaller infarct and fewer reperfusion arrhythmias in a rat model of ischemia and reperfusion injury *in vivo* [21].

It is well known that the degree of LV remodeling is influenced by infarct size. One-time IV administration of CoQ_{10} limited the size of the infarct zone and subsequent LV remodeling. Significant correlations between the parameters of cardiac function and myocardial concentrations of CoQ_{10} were found, demonstrating that higher myocardial levels of CoQ_{10} were accompanied by better-preserved LV function (Figure 3B). Although high levels of CoQ_{10} were sustained for at least 3 weeks after a single IV injection in all CoQ_{10}-treated groups, limited LV damage and dilatation and significantly improved cardiac systolic and diastolic function were observed only in the 60-min series, suggesting that the crucial factor in CoQ_{10} administration is time from MI onset rather than its quantity 21 days after.

Cardiac remodeling occurred following cessation of flow in the occluded coronary artery. Without interruption, this process progresses and causes heart failure, the severity of which is a significant factor in prognosis [22]. Oxygen depletion and myocyte death activate the excessive generation and accumulation of free radicals and the inflammatory process, the main links in the pathogenesis of post-infarction LV remodeling [23,24]. Oxidative stress, depleted antioxidant defenses, and increased lipid peroxidation and production of proinflammatory mediators, are key factors in acute myocardial injury. Imbalance in the formation of reactive oxygen species initiates lipid peroxidation and damage of cell membranes, resulting in rupture of mitochondria and lysosomes with subsequent apoptosis or necrosis. It is known that suppression of both free radical formation and the intensity of inflammatory response can limit myocardial ischemic damage [25,26].

Without intervention, a portion of the myocardium in the supply region of the occluded artery is inevitably lost. However, the myocardium adjacent to the infarct area develops collateral vessels, which can deliver substances for the protection and preservation of heart muscle in the area at risk. Any beneficial strategy will provide compromised cells with agents that can maintain viable myocardium and prevent necrosis in the area at risk and limit subsequent ventricular remodeling and post-infarction heart failure.

CoQ_{10} is known to neutralize excessive formation of reactive oxygen species by suppression of NADPH oxidase expression; scavenging lipid peroxides and preventing nitrative stress through inhibition of excess NO production [27-29]. CoQ_{10} shows anti-inflammatory features by

limiting the release of proinflammatory mediators during inflammatory response [30]. It is known that an increase in tumor necrosis factor (TNF)-α is an important step in activation of the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which is responsible for injury during inflammatory reactions [31]. Suppression of TNF-α production and NF-κB activation are effective in defending the heart against injury. There is evidence that CoQ_{10} reduces excessive formation of TNF-α and the expression of NF-κB and inducible nitric oxide synthase (iNOS) [32]. The beneficial effects of CoQ_{10} could be due to its potential to inhibit the activation of NF-κB signaling pathway and subsequent transcription of NADPH oxidase, TNF-α, and iNOS genes [33,34]. One of possible protective action of CoQ_{10} could be inhibition of mitochondrial permeability-transition pore opening [35].

It has been suggested that food intake of CoQ_{10} leads to increasing blood levels when tissue content is not changed [8]. Maximal myocardial content of CoQ_{10} after IV administration of a CoQ_{10}-loading-microsphere delivery system has been observed 60 min after injection, with no differences at other time-points up to 12 h [36]. Oral intake requires a long-term preventive course to increase cell CoQ_{10} concentration enough to derive it effects.

The cardioprotective effects of CoQ_{10} administration have been studied only as preventive treatment of ischemia-reperfusion injury mostly *in vitro* in isolated hearts in an *in vivo* study with intracoronary administration or long-term oral intake and cardioprotective effects of CoQ_{10} were either shown or not [10-12,19, 20,37, 38].

Long-term oral administration of CoQ_{10} has been shown to increase SV, EF, CO, EDV and increased plasma CoQ_{10} levels have been accompanied by notable improvement of patients with congestive heart failure CHF [4,39]. To render the protective effects of ubiquinone, its content in myocardium should be notable increased. In most studies, administration of exogenous CoQ_{10} caused substantial increases in plasma levels of ubiquinone [40-43]. A more complicated issue is elevation of CoQ_{10} content in myocardium: a small increase in myocardial homogenates, a selective increase in mitochondrial CoQ_{10} levels only and a complete lack of CoQ_{10} increase in myocardium have all been observed [8,40-43]. These resulted from different doses, and routes and durations of CoQ_{10} administration, and all of these factors have a decisive influence on tissue bioavailability. Intravenous injection of CoQ_{10} ensure maximum tissue bioavailability to provide cardioprotection.

Conclusion

A single IV injection of solubilized CoQ_{10} (30 mg/kg) to limit LV myocardial damage and deterioration of function is effective when administered at minute 60 after coronary ligation but not at minute 180. CoQ_{10} injected at minute 60 after coronary artery occlusion limited infarct zone and subsequent LV remodeling as measured by improvement in cardiac function on postoperative day 21, at which point levels of CoQ_{10} in myocardium, liver, and plasma were still elevated and correlated with LV volumes and systolic and diastolic indexes. The development of parenteral forms of CoQ_{10} for urgent therapy of cardiovascular events could be beneficial.

Acknowledgments

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