Single Intravenous Injection of Coenzyme Q_{10} Protects the Myocardium after Irreversible Ischemia

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Experiments were performed on the model of irreversible myocardial ischemia in Wistar rats. Coenzyme Q_{10} was injected intravenously 10 min after coronary artery occlusion. On day 21 after myocardial infarction the content of coenzyme Q_{10} in the left ventricle, liver, and plasma from animals of the treatment group was higher than that in untreated rats by 23, 1042, and 87%, respectively ($p<0.05$). The area of the necrotic zone was lower, and postinfarction hypertrophy of the left ventricle was less pronounced in coenzyme-receiving rats. Right ventricular hypertrophy did not develop in these animals. These rats were characterized by greater stroke volume (by 24.6%, $p<0.05$), stroke work (by 34.9%), cardiac output (by 37.8%, $p<0.05$), ejection fraction (by 35.7%, $p<0.05$), and contractility (by 22.5%, $p<0.05$), but lower end-diastolic pressure (by 25.8%, $p<0.05$) than untreated animals. These data indicate that the development of parenteral ubiquinone preparations holds much promise for urgent therapy of acute cardiovascular disorders.

Key Words: *coenzyme Q10; intravenous injection; myocardial infarction; hypertrophy; left ventricular hemodynamics*

There is a large body of evidence that coenzyme Q10 (CoQ_{10}, ubiquinone) can be recommended for additional therapy of various cardiovascular diseases (chronic heart failure, hypertension, myocardial infarction, *etc*.) [5,7,8,10]. Previous studies on the model of irreversible myocardial ischemia showed that long-term preventive oral treatment with CoQ_{10} is followed by a decrease in the infarction area and reduction of postinfarction myocardial hypertrophy [2]. CoQ_{10} concentration in the myocardium should be rapidly increased to protect the heart from ischemic injury in emergency states. Intravenous injection of CoQ_{10} is optimal for this purpose. Due to lipophilicity of CoQ_{10}, there are no medicinal forms for intravenous administration of this compound. Individual experimental studies for the efficiency of preventive intracoronary infusion of CoQ_{10}-loaded liposomes demonstrated a potent protective effect of this form during myocardial infarction [14].

Here we studied the efficiency of urgent increase in the content of CoQ_{10} in the myocardium (intravenous injection of solubilized CoQ_{10}) in protecting the myocardium from irreversible ischemia.

MATERIALS AND METHODS

Experiments were performed on Wistar rats with experimental irreversible ischemia of the myocardium due to left coronary artery occlusion. The animals received a single intravenous injection of 30 mg/kg CoQ_{10} (Kudesan Rastvor, Akvion; infarction+CoQ_{10} group, n=12) or 1 ml/kg physiological saline (infarction group, n=11) 10 min after occlusion. Sham-operated rats (non-tied ligature, n=7) were treated with 1 ml/kg physiological saline.

The effects of intravenous injection of CoQ_{10} were evaluated from functional characteristics of the heart, content of CoQ_{10} in the plasma, myocardium,

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and liver, severity of myocardial injury, and degree of postinfarction hypertrophy on day 21 after occlusion.

Intracardiac hemodynamics was studied using a Millar SPR-838 catheter (Millar Instruments) [9]. The catheter was inserted into the left ventricle (LV) of anesthetized rats (sodium pentobarbital, 45 mg/kg intraperitoneally) during closed-chest surgery. A blood pressure sensor and 4 electrodes for the measurement of LV volume were located at the end of the catheter. The study was performed on a Pressure Volume Conductance System (Chart5 and PVAN 3.5 software; Millar Instruments). The blood was sampled after hemodynamic measurements. The sample was centrifuged. The plasma was stored at -20°C. The weight indexes of the left and right ventricles were calculated as the ratio of the ventricular weight (g) to body weight of the animal (kg). LV was cut into 5 longitudinal sections from the apex to the base. These sections were placed into 1% triphenyltetrazolium chloride in phosphate buffer (pH 7.4) at 37°C for 15 min. The necrotic zone was studied planimetrically. Quantitative assay of CoQ_{10} in tissues was performed by the method of HPLC with electrochemical detection [2].

The results were analyzed by the Mann—Whitney test (Statistica 6.0 software). The data are presented as the means and standard deviations of the means.

RESULTS

The pressure-volume curves of anesthetized rats were constructed on day 21 after occlusion (Fig. 1) and parameters of cardiac function were calculated from these curves (Table 1).

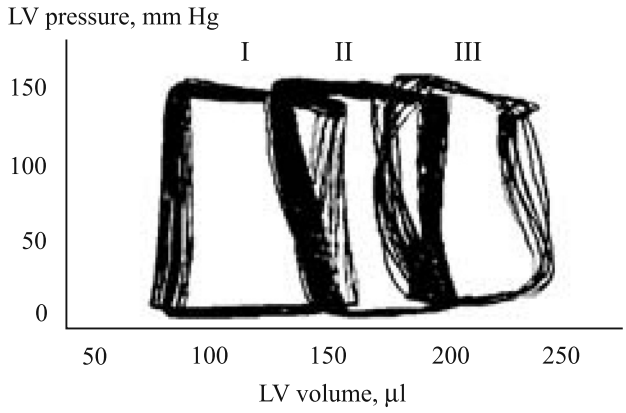

Fig. 1. Pressure-volume diagrams for the sham-operation (I), infarction (II), and infarction+CoQ_{10} groups (III) on day 21 after modeling of myocardial infarction.

Irreversible myocardial ischemia was followed by a significant decrease in the stroke volume, cardiac output, ejection fraction, and myocardial contractility, lengthening of the LV relaxation period, and increase in the end-diastolic pressure (as compared to sham-operated animals; Fig. 2). Administration of CoQ_{10} reduced the degree of systolic and diastolic dysfunction and prevented changes in the stroke volume, cardiac output, stroke work, and end-diastolic pressure (no differences from sham-operated animals; Fig. 2, Table 1).

Connective tissue aneurisms were formed in the area of blood supply of an occluded artery in untrea-

TABLE 1. Hemodynamic Indexes and Parameters of Systolic and Diastolic Function Calculated from the Pressure-Volume Ratio in Rats

Hemodynamic index	Group		
	sham-operated	infarction	infarction+CoQ_{10}
HR, bpm	377±47	348±52	356±31
End-systolic volume, μl	99±4	173±50*	129±44
End-diastolic volume, μl	180±9	255±62*	234±58*
End-systolic pressure, mm Hg	128±6	130±31	134±20
End-diastolic pressure, mm Hg	7.9±1.7	10.6±2.3*	7.9±1.2+
Stroke volume, μl	95.1±4.9	73.7±18.2*	91.9±17.0+
Ejection fraction, %	49.7±2.6	30.3±7.1*	41.1±4.4*+
Cardiac output, ml/min	38.1±3.4	23.5±6.4*	32.3±5.7+
Stroke work, mm Hg/μl	8.2±1.3	6.3±1.8*	8.5±1.5+
Myocardial contractility, mm Hg/sec	10 404±725	7273±1543*	8911±1631*+
Myocardial relaxation, mm Hg/sec	10 991±1517	5150±520*	7198±1540*+

Note. Here and in Table 2: $p<0.05$: *compared to sham-operation; +compared to infarction.

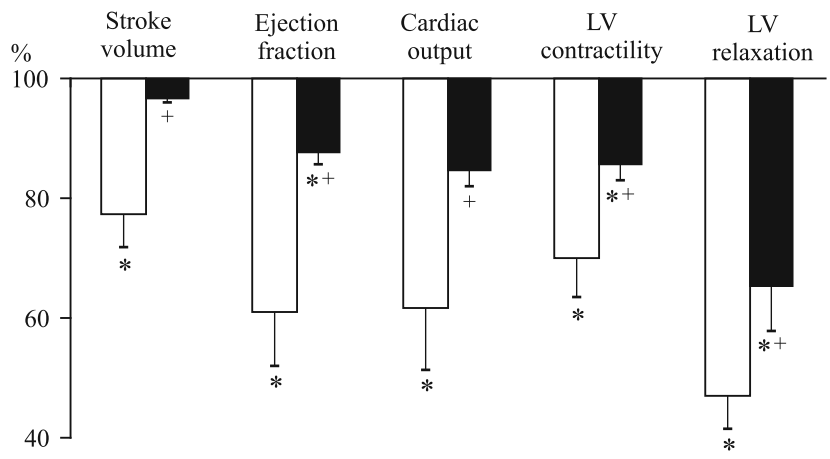

Fig. 2. Functional characteristics of intracardiac hemodynamics in the infarction (light bars) and infarction+CoQ_{10} groups (dark bars) relative to the sham-operation group (100%). $p<0.05$: *compared to the sham-operation group; +compared to the infarction group.

ted animals. These aneurisms completely substituted for the muscular wall. In CoQ_{10}-receiving animals, postinfarction scars were localized in the ischemic myocardial wall.

Myocardial infarction was followed by LV hypertrophy. These changes were less pronounced in CoQ_{10}-treated animals (Table 2). Right ventricular hypertrophy was observed only in untreated animals.

On day 21 after myocardial infarction, the content of CoQ_{10} in the myocardium, plasma, and liver from animals of the infarction+CoQ_{10} group was higher than that in rats of the infarction group by 23 ($p<0.05$), 87 ($p<0.01$), and 1042% ($p<0.001$), respectively.

These data indicate that single intravenous injection of solubilized CoQ_{10} solution increased the concentration of CoQ_{10} not only in the plasma, but also in the myocardium and liver. It should be emphasized that elevated plasma concentration of CoQ_{10} on day 21 after single injection cannot result from long-term circulation in the blood (taking into account the pharmacokinetic characteristics). A persistent increase in plasma CoQ_{10} concentration is probably related to a 10-fold rise in the amount of this substance in the liver. This organ is involved in ubiquinone synthesis to maintain the endogenous pool of these compounds in blood plasma. The increase in plasma CoQ_{10} concentration contributes to the elevated content of this substance in the myocardium.

Single intravenous injection of CoQ_{10} after coronary artery occlusion reduces the degree of postinfarction LV hypertrophy. The myocardium of the left and right ventricles is involved in late remodeling in animals of the infarction group. Right ventricular hypertrophy does not develop in animals of the infarction+CoQ_{10} group due to partial compensation of LV function.

The use of intracardiac catheter allowed us to perform a simultaneous and continuous measurement of LV volume and pressure. Hemodynamic changes were observed on day 21 after modeling of myocardial infarction. Postinfarction changes in heart function are described in details from characteristics of the LV pressure-volume (PV) loop. The efficiency of cardioprotective drugs can be compared taking into account these data and results of a morphological study of the myocardium. In untreated animals, a rightward shift of the PV loop along the volume axis illustrates an increase in the LV volume due to substitution of the muscle tissue for the connective tissue and aneurism formation. The increase in the end-diastolic pressure and lengthening of the LV relaxation period are typical of diastolic dysfunction, which serves as one of the earliest sign for heart failure.

Functional indexes of the myocardium in animals of the infarction+CoQ_{10} group were higher than those in untreated rats. Therefore, single intravenous injec-

TABLE 2. Weight Indexes of the Left (LV) and Right Ventricles (RV) in Rats of Various Groups

Parameter	Group		
	sham-operated	infarction	infarction+CoQ_{10}
Weight index of LV, g/kg	1.84±0.70	2.17±0.11*	2.03±0.15*+
Weight index of RV, g/kg	0.48±0.04	0.59±0.10*	0.47±0.07+

tion of CoQ_{10} after coronary artery occlusion contributes to the maintenance of systolic and diastolic functions and reduces the degree of late postinfarction remodeling of LV. It was manifested in a less significant increase in the end-systolic and end-diastolic volume due to a lower dilation of LV.

Clinical studies for the efficiency of long-term oral treatment with CoQ_{10} preparations showed that this substance increases the stroke volume, ejection fraction, cardiac index, and end-diastolic volume [10]. The increase in plasma CoQ_{10} concentration is associated with the improvement of patients with chronic heart failure [5]. The mechanisms for cardioprotective activity of CoQ_{10} were evaluated in some studies. Published data show that CoQ_{10} protects the myocardium from consequences of ischemia, which is associated with an increase in the energy and antioxidant state [6,13,15]. The influence of CoQ_{10} on the inflammatory response is related to the inhibition of TNF-α secretion [1,11], whose level increases after the incidence of infarction [3,4]. It should be emphasized that the decrease in TNF-α concentration is followed by the reduction of myocardial necrosis [12].

We conclude that single intravenous injection of CoQ_{10} over the first few minutes after myocardial ischemia provides a long-term increase in CoQ_{10} concentration in the plasma and myocardium of rats (probably due to storage in the liver). These changes result in a significant decrease in the severity of systolic and diastolic dysfunction, area of the necrotic zone, and degree of postinfarction LV hypertrophy and prevention of postinfarction right ventricular hypertrophy. These data indicate that the development of parenteral ubiquinone medicines holds much promise for urgent therapy of acute cardiovascular disorders.

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