UBIQUINONE PLASMA LEVELS ARE CORRELATED WITH BRAIN NATRIURETIC PEPTIDE PLASMA LEVELS IN PATIENTS WITH CHRONIC HEART FAILURE: THE POTENTIAL OF COENZYME Q10 COMBINED THERAPY

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POVEZANOST PLAZMA NIVOA UBIHINONA SA NIVOEM MOŽDANOG NATRIURETSKOG PEPTIDA KOD PACIJENATA SA HRONIČNOM BOLEŠĆU SRCA: EFEKTI KOMBINOVANE TERAPIJE KOENZIMOM Q10

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Received / Primljen: 22.04.2018. Accepted / Prihvaćen: 24.04.2018

ABSTRACT

Despite the association of a worse HF-related clinical status with lower CoQ10 levels, the prognostic use of CoQ10 is controversial. The aim of this study is to optimize pharmacotherapy for patients with ischaemic CHF, based on the clinical and functional parameters of the heart and brain natriuretic peptide (BNP) plasma levels, which are correlated with the CoQ10 plasma levels, and to assess patient prognosis after receiving CoQ10 therapy. This prospective clinical study included 75 patients aged 56 to 63 years old with coronary heart disease (CHD) classified as class I–III according to the NYHA classification. After assessment of the clinical-instrumental characteristics of the CVD course (complaints, medical history, physical examination, a 6-minute walk test, echocardiography, and test for reactive hyperaemia), we determined the BNP level and CoQ10 plasma levels. At the same time, we assessed the efficacy of CoQ10 treatment (at a dose of 60 mg/per day) and tolerability in CVD-combined therapy during a follow-up of 12 weeks. CoQ10 supplementation in HF patients induced improvements in their functional cardiac parameters, such as the ejection fraction. Our results suggest that supplemental CoQ10 may be a useful option for effective management of heart failure and warrant future adequately powered randomized controlled trials of CoQ10 supplementation in patients with HF.

Key words: *coenzyme Q10-combined therapy, brain natriuretic peptide, chronic heart failure*

SAŽETAK

Uprkos povezanosti lošeg HF kliničkog statusa sa nižim nivoima CoQ10, prognostička upotreba CoQ10 je kontroverzna. Cilj ove studije je razviti optimalnu farmakoterapiju za pacijente sa ishemijskom bolešću srca na osnovu kliničkih i funkcionalnih parametara srca i plazma nivoa natriureznog peptida B, koji je koreliran sa plazma nivoom CoQ10, kao i da se proceni ishod terpije CoQ10 (BNP). Ova prospektivna klinička studija uključila je 75 pacijenata starosti od 56 do 63 godina zivota sa koronarnom bolešću srca (CHD) klasifikovanim kao NIHA klasa I-III. Nakon procene kliničkih karakteristika CVD statusa (simptomi, medicinska istorija, fizički pregled, 6-minutni test hoda, ehokardiografija, test sa reaktivnom hiperemijom), merili smo nivoe BNP i CoQ10 u plazmi. Istovremeno, procenili smo efikasnost terapije CoQ10 (u dozi od 60 mg/dnevno) i toleranciju u kombinovanoj CVD terapiji tokom 12 nedelja. Suplementacija CoQ10 kod pacijenata sa HF je dovela do poboljšanja funkcionalnih parametara srca, kao što je ejekciona frakcija. Naši rezultati sugerišu da suplementacija CoQ10 može biti korisna opcija za efikasno upravljanje srčanim popuštanjem i obezbeđuju osnovu za buduće randomizirane i kontrolisane studije koje bi ispitivale suplementaciju CoQ10 kod pacijenata sa HF.

Kljucne reci: *koenzim Q10 kombinovana terapija, mozdani nstriurezni peptid, hronična bolest srca*

UDK: 615.356:577.161.6; 616.12-036.1-085.356
Ser J Exp Clin Res 2018; 19 (2): 141-149;
DOI: 10.2478/SJECR-2018-0012

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INTRODUCTION

In recent decades, the dominance of cardiovascular diseases (CVD), as major contributors to the total mortality of the employable population, has emerged. Chronic heart failure (CHF) plays a special role in the death rate because of its unfavourable course and prognosis. The results of the Framingham Heart Study indicated that CHF patients make up 2.5 percent of all Americans above 45 years of age or 5 million cases in total (550,000 new cases of CHF per year) (1, 2).

The current understanding of CHF pathophysiology is best described by the neurohormonal hypothesis. The use of renin-angiotensin-aldosterone system inhibitors and beta-blockers in clinical practice has led to a reliable reduction of total and cardiovascular mortality in patients with CHF (3, 4). However, apart from neurohormonal activation, increased production of pro-inflammatory cytokines following the immunoinflammatory response and initiation of lipid peroxidation play important roles in the pathophysiology of CVD. Increased reactive oxygen species (ROS) production leads to endothelial injury and reduction of nitric oxide production, triggers apoptosis, and has a negative inotropic effect (5, 6).

A potential treatment that option focuses on reducing symptoms and improving quality of life and prognosis of patients with CVD is the correction of myocardial oxidative injury by means of CoQ10 therapy (7). Coenzyme Q10 (CoQ10) is an endogenously synthesised and diet-supplied lipid-soluble cofactor that functions in the mitochondrial inner membrane to transfer electrons from complexes I and II to complex III (6, 7). Coenzyme Q10 (CoQ10), which is present in all cells of the human body, is essential for adenosine triphosphate (ATP) synthesis (5, 8). The reference range of reduced CoQ10 for children (younger than 18 years of age) is 320–1376 μg/L and for adults (aged 18 years or older) is 415–1480 μg/L. The reference values for total CoQ10 for children and adults are 320–1558 μg/L and 433–1532 μg/L, respectively. The normal percentage of reduced CoQ10 in children varies from 93% to 100%, while in adults, it falls between 92% and 98% (8).

Under experimental conditions, it was also shown that apart from increased reactive oxygen species production, CVD is accompanied by suppression of myocardial antioxidant systems (9). In the case of high levels of oxidative stress, CoQ10 reduces the nitric oxide inactivation rate (wherein NO is converted into peroxynitrite), thus protecting the vascular wall (10). It is well known that tissues with high energy requirements or metabolic activity, such as the heart, liver, kidneys, and muscles, contain the highest concentrations of CoQ10 (6, 9). Cardiomyocytes contain the highest concentration of ubiquinone due to their high energy requirements. It was established that plasma CoQ10 is progressively reduced with the increasing severity of CVD (11, 12).

Biomarker identification is a possible approach to estimating the severity of CVD and assessing its prognosis. In this procedure, determination of the B-type of brain natriuretic peptide plasma levels is conducted (13, 14). Increased levels of BNP are identified as an independent assessment criterion of CVD severity and a mortality predictor of CVD (13, 14).

Preclinical data have provided information across a variety of models that support the pathophysiological role of CoQ10 depletion in HF and other cardiovascular diseases as well as the concept of improved outcomes with CoQ10 supplementation (15). A meta-analysis of 13 randomized, controlled, blind trials indicated that CoQ10-combined therapy significantly improved the New York Heart Association (NYHA) functional class, increased physical activity tolerance, and reduced the number of hospitalizations due to CHF decompensation (16, 17). A number of studies indicate that application of CoQ10 at a daily dose of 100 – 200 mg results in increased contractility of the heart muscle (18). However, the results of some studies have been equivocal (18, 19). The possible reason for the limited efficacy of CoQ10-combined therapy may be the use of low doses.

There have been a large number of trials examining the effect of CoQ10 in HF conducted over the past 30 years. Despite the association of a worse HF-related clinical status with lower CoQ10 levels, the prognostic use of CoQ10 is controversial. The aim of this study is to develop pharmacotherapy optimization for patients with ischaemic CHF based on the clinical and functional parameters of the heart and brain natriuretic peptide (BNP) plasma levels, which are correlated with the CoQ10 plasma levels, and to assess patient prognosis after CoQ10 therapy.

PATIENTS AND METHODS

Ethical Approval

All patients before inclusion in the study provided informed consent. The study was approved by the Committee of Ethics of the local institution (IM Sechenov First Moscow State Medical University, Moscow, Russia) and conducted according to the principles of the Declaration of Helsinki.

Patients and study design

This prospective clinical study included 75 patients aged 56 to 63 years old with (CHD) classified as class I–III according to the NYHA classification. The inclusion criteria were the presence of CHF symptoms, left ventricular ejection fraction under 45% as confirmed by echocardiography and a previous myocardial infarction. Patients who were on standard therapy (beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, diuretics, statin nitrates and antiplatelet therapy) were also included.

After assessment of the clinical-instrumental characteristics of the CVD course (complaints, medical history, physical examination, a 6-minute walk test, echocardiog-

raphy, and a test for reactive hyperaemia), we determined the levels of BNP and plasma CoQ10. At the same time, we assessed the efficacy of the CoQ10 treatment (at a dose of 60 mg/per day) and its tolerability in CVD-combined therapy during a follow-up of 12 weeks. The efficacy and tolerability of the CoQ10-combined therapy was assessed according to the clinical manifestation dynamics of CHF, CHF functional class (NYHA), exercise tolerance, morphological and functional cardiac parameters and changes in plasma concentrations of NT-proBNP and CoQ10. All of the abovementioned parameters were assessed two times, at the beginning of the study (baseline) and after 12 weeks of follow-up.

Assessment of the patient clinical status

Assessment of the patient clinical status was based on analyses of complaints, a physical examination, the results of a 6-minute walk test, and morphological and functional parameters of the heart on echocardiography.

To assess endothelial-dependent vasodilatation, a Doppler evaluation of changes in the brachial artery diameter during reactive hyperaemia (HR) was used. The results were considered satisfactory if the brachial artery diameter, following the release of reactive hyperaemia, increased by more than 10%. In the case of a negative test result, endothelial dysfunction was diagnosed.

Biochemical analyses

Determination of N-terminal pro B-type natriuretic peptide (NT-proBNP)

The determination of the N-terminal pro B-type natriuretic peptide (NT-proBNP) plasma level was carried out using an automated immunochemiluminescence assay based on the sandwich principle ("Biomedica NT-proBNP") (20).

Determination of Coenzyme Q10 plasma levels

The determination of the Coenzyme Q10 plasma level was carried out using an isocratic method of reverse-phase high-performance liquid chromatography (HPLC). We used the Stayer liquid chromatograph system, Akvilon, Russia, Phenomenex Luna, with a 5 μm, 4.6×150 mm C18 column and ESA Coulochem II 5010 Electrochemical Detector. Chromatogram registration and processing were performed using the Environmental Sciences Associate, Inc., USA software (21).

Statistical analyses

Statistical analyses were carried out with the software package SPSS 11.5 for Windows. Nonparametric methods were used in the case of a non-Gaussian distribution of data, andalong with Spearman correlation analysis, the Wilcoxon test for paired comparisons, and the median test (a special case of the chi-square test used for multiple independent samples). The linear relationship intensity between independent and dependent variables, accounted for the influence of other variables and, was determined via multiple linear regression analysis. Data are presented as the median (Me) and range of the upper and lower quartiles based on a non-parametric distribution of data. Differences were considered significant at $p<0.05$.

RESULTS

Socio-demographic and clinical characteristics of the study group

This study consisted of 75 CHF patients with NYHA class I–III caused by coronary heart disease (54 males and 21 females, with an average age of 61.5). The proportions of patients with NYHA classes I, II, and III were 20% (15 patients), 64% (48 patients), and 16% (12 patients), respectively. All patients developed CHF due to coronary heart disease, with an average disease duration of 46.0 months (from 16 to 96 months). All patients received standard therapy: beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, diuretics, and statins; 25% of patients received nitrates, and 92.6% of patients received antiplatelet therapy (Table 1).

According to the 6-minute walk test, there was a significant reduction in physical activity tolerance in patients (the average distance was 385.5 m). Morphological and functional changes in cardiac parameters were sufficiently pronounced in all patients (with an average left ventricular ejection fraction of 38.2%). Complaints analysis and physical examination revealed that 80% of CHF patients (60 patients) had NYHA II-III prior to the study. According to the 6-minute walk test, the average distance was 385.5 m (354.0; 407.5), which corresponds to the a reduction in physical activity tolerance in patients with NYHA class II (Table 1). According to the echocardiographic data, the average left ventricular ejection fraction (LVEF) was 38.2% (33.4; 43.1). The average NT-proBNP plasma level was 240.3 pg/mL (70.83; 524.32), which corresponded to a normal level of this peptide in CVD patients (the plasma level

Table 1. Demographic characteristics of the study population

Number of patients	75
Males/females, n (%)	54 (72%); 21 (28%)
Average age (years)	61.5 (range 56-63)
CHF duration (months)	46.0 (24; 79)
NYHA classes I/II/III, n (%)	15 (20)/ 48 (64)/ 12 (16)
Coronary heart disease, n (%)	75 (100)
Previous myocardial infarction, n (%)	75 (100)

Table 2. Clinical parameters of the study population

Left ventricular ejection fraction, %	38.2 (33.4; 43.1)
Average 6-minute walk test distance, m	385.5 (354.0; 407.5)
CoQ10 plasma levels, ng/mL	826.3 (510.8; 1080.3)
NT-proBNP average plasma level, pg/mL	240.3 (70.83; 524.32)
Brachial artery diameter at rest, cm	0.51 (0.43; 0.56)

Table 3. Brachial artery diameter during reactive hyperaemia according to ultrasound images

	Normal vasodilatation following reactive hyperaemia	Moderate endothelial dysfunction	Significant endothelial dysfunction
Number of patients, n (%)	12 (16%)	40 (53.3%)	23 (30.7%)
Initial diameter of the brachial artery at rest, cm	0.57 (0.54; 0.59)	0.56 (0.55; 0.59)	0.57 (0.53; 0.60)
Diameter of the brachial artery following reactive hyperaemia, cm	0.65 (0.59; 0.66)	0.59 (0.57; 0.60)	0.58 (0.56; 0.61)
Brachial artery diameter increase, %	12.5	7.3	2.6
CoQ10 concentration, ng/Ml	1451.3 (1106.2; 1593.8)	1051.7 (702.5; 1239.0)	904.6 (678.2; 1027.5)
Percentage of patients with CoQ10 concentration of less than 700 ng/mL	41.7	45	52.2
NT-proBNP, pg/mL	216.8 (139.2; 404.5)	232.1 (153.4; 472.7)	283.1 (192.6; 523.8)
NYHA class	2.1	2.5	2.7
Ejection fraction, %	43.2 (39.2; 44.1)	40.0 (37.4; 42.9)	38.4 (35.7; 42.3)

was higher than that in healthy persons (0 – 125 pg/mL)). The initial average CoQ10 concentration was 826.3 ng/mL in all patients.

Association of the Doppler evaluation of endothelial-dependent vasodilatation and the clinical, morphological, and functional features of CHF patients

According to the Doppler evaluation of the brachial artery diameter, the initial diameter of the brachial artery was 0.51 cm (Table 3). The results of the Doppler evaluation of changes in the brachial artery diameter during reactive hyperaemia showed that only 12 patients (16%) had a proper increase in brachial artery diameter after the test and 63 patients (84%) had endothelial dysfunction. Additionally, 40 patients (53.3%) had moderate endothelial dysfunction with an increase in the brachial artery diameter from 5 to 10%, and 23 patients (30.7%) had severe endothelial dysfunction with an increase in the brachial artery diameter of less than 5%.

Taking into account that CoQ10 deficiency causes endothelial dysfunction; endothelial-dependent vasodilatation was assessed in all patients. Correlating the results of the ultrasound images of the brachial artery diameter following reactive hyperaemia and the CoQ10 concentration revealed that, poor endothelial-dependent vasodilatation caused by endothelial dysfunction in patients with CHF was accompanied by a reduction in the plasma CoQ10 concentration. There was evidence that the lower the CoQ10 concentration the higher the severity of endothelial dysfunction. Moreover, a correlation between the severity of endothelial dysfunction and the clinical morphological and functional characteristics was noted. Patients with a normal brachial artery diameter following reactive hyperaemia vasodilation had a higher level of the left ventricular ejection fraction (43.2% against 40.5 or 38.4%) and lower level of the average NYHA class (2.1 against 2.5 and 2.7) than patients with moderate to significant endothelial dysfunction (the differences were not significantly reliable). Moreover, the higher the level of endothelial dysfunction, the lower the LVEF and higher the NYHA class. Similar features were also observed when comparing the NT-proBNP plasma concentration with the severity of endothelial dysfunction: patients who were normal following reactive hyperaemia vasodilatation had a lower average NT-proBNP concentration (216.8 (139.2; 404.5)) than patients with moderate (232.1 (153.4; 472.7)) and significant (283.1 (192.6; 523.8)) endothelial dysfunction (Table 3).

Association of the NT-proBNP and the clinical, morphological, and functional features of CHF patients

The average NT-proBNP plasma concentration was 240.3 pg/mL (70.83; 524.32); nevertheless, the scatter of values was significant (from 20.2 to 860.0 pg/mL). To analyse the clinical, morphological, and functional features of CHF patients with different plasma levels of NT-proBNP, two groups of patients were identified: the first group consisted of CHF patients with NT-proBNP plasma levels of less than 125 pg/mL; the second group consisted of CHF patients with NT-proBNP plasma levels of more than 125 pg/mL. The characteristics of CHF patients that depended on the NT-proBNP plasma levels are shown in *Table 4*.

Table 4. Characteristics of CHF patients that depend on the NT-proBNP plasma levels

	CHF patients with NT-proBNP plasma levels less than 125 pg/mL	CHF patients with NT-proBNP plasma levels more than 125 pg/mL	*p*
Number of patients, n (%)	15 (20)	60 (80)	-
Average age, years	64.5 (59.0; 66.5)	63.0 (59.5; 69.0)	*0.98*
Males/females, n (%)	9(60) / 6(40)	45 (80) / 15 (20)	*0.48*
Average NT-proBNP plasma level, pg/mL	62.2 (49.8; 104.4)	264.16 (177.4; 491.9)	*0.001*
Average distance according to the 6-minute walk test, m	405.0 (393.0; 427.0)	336.5 (300.75; 408.0)	*0.079*
LVEF, %	42.7 (39.5; 44.3)	38.2 (36.3; 43.1)	*0.001*
Average CoQ10 plasma level, ng/mL	1020.0 (744.4; 1217.0)	631.6 (403.2; 972.5)	*0.228*

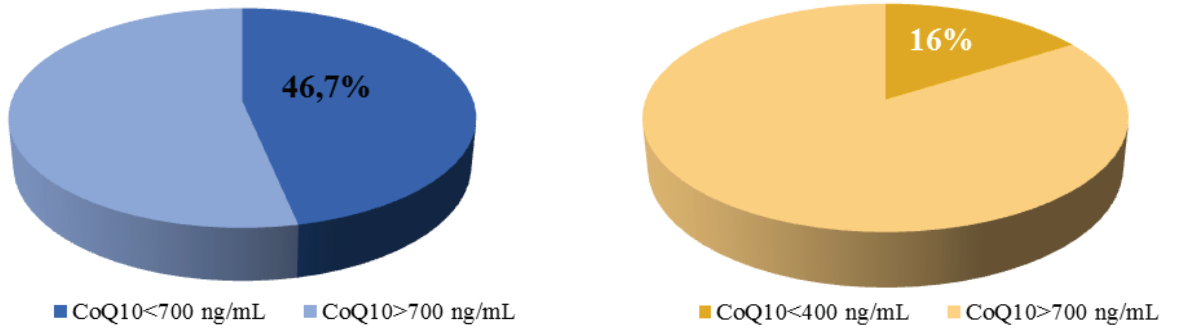

Figure 1. Percentage of CHF patients with low CoQ10 plasma levels

The difference in patient age was not significantly reliable, but the first group was characterized by a significantly higher number of women than the second (40% against 20%). All patients from the first group were diagnosed with CHF I NYHA class and had an average walk distance of 450.0 meters (393.0; 427.0) according to the 6-minute walk test. In the second group, the average distance according to the 6-minute walk test (336.5 meters) was less than the average distance recorded for the first group, and (300.8; 408.3) (p=0.079), which corresponded to an average distance according to the 6-minute walk test in patients with NYHA classes II and III. Significant differences were observed in the contractile function of the left ventricle (p=0.001): there was a significantly higher level of systolic function in the first group (LVEF 42.7 (39.5; 44.3)) and lower level in the second group (LVEF 38.2 (36.3; 43.1)) (p=0.001), according to the echocardiography results. No significant differences were observed in the CoQ10 plasma levels; however, there was a very slight trend towards significance: the average CoQ10 plasma level was 1020.0 ng/mL (744.4; 1217.0) in the first group and 631.6 n/mL (403.2; 972.5) in the second group (p=0.228).

Association of the coenzyme Q10 plasma concentration and the clinical, morphological, and functional features of CHF patients

In this study, we found a wide variety of CoQ10 plasma levels in CHF patients: 350 ng/mL to 1903 ng/mL. However, 35 patients (46.7%) had CoQ10 plasma levels less than 700 ng/mL, and 12 patients (16%) had CoQ10 plasma levels that were even lower (less than 400 ng/mL) (Fig. 1).

To analyse the clinical, morphological, and functional features of CHF patients with normal and low CoQ10 plasma levels, two groups of patients were identified. The first group consisted of CHF patients with CoQ10 plasma levels lower than 700 ng/mL (the average concentration was 513.1 ng/mL (442.5; 619.5)). The second group consisted of CHF patients with CoQ10 plasma levels higher than 700 ng/mL (the average concentration was 1042.0 ng/mL (960.0; 1283.5); p=0.001). The analysis of the CHF patient clinical and demographic features of CHF patients with initially normal and low CoQ10 plasma levels showed that there was a variety of non-significant differences in these groups (*Table 5*). There were more males than females in both groups (with no significant differences), and patients with lower CoQ10 plasma concentrations were younger than patients with normal CoQ10 plasma concentrations (there was a slight trend towards significance).

Patients with lower CoQ10 plasma levels had less CHF history and higher NYHA class (but these differences were not significant). Patients in this group had a more severe course of chronic heart failure: the average distance according to the 6-minute walk test was significantly lower (there was a trend towards significance) than average the distance in patients with normal CoQ10 plasma levels. Compared to patients with normal CoQ10 plasma levels, patients with lower CoQ10 plasma levels had non-significant higher NT-proBNP plasma levels and lower LVEFs.

Table 5.CHF patient characteristics depending on CoQ10 plasma levels

	CoQ10<700 ng/mL	CoQ10>700 ng/mL	*p*
Number of patients, n (%)	35 (46.7)	40 (53.3)	-
Average age, years	58.0 (54.0; 66.0)	63.0 (60.5; 70.0)	*0.18*
Males/females, n (%)	24(68.6) / 11(31.4)	30 (75) / 10 (25)	*0.82*
Average NT-proBNP plasma level, pg/mL	156.4 (121.2; 220.4)	105.68 (53.7; 240.7)	*0.221*
Average distance according to the 6-minute walk test, m	336.5 (307.3; 387.5)	405.0 (340.5; 432.0)	*0.059*
LVEF, %	39.5 (37.5; 43.0)	42.0 (40.5; 44.0)	*0.58*
Average CoQ10 plasma level, ng/mL	513.1 (442.5; 619.5)	1042.0 (960.0; 1283.5)	*0.001*

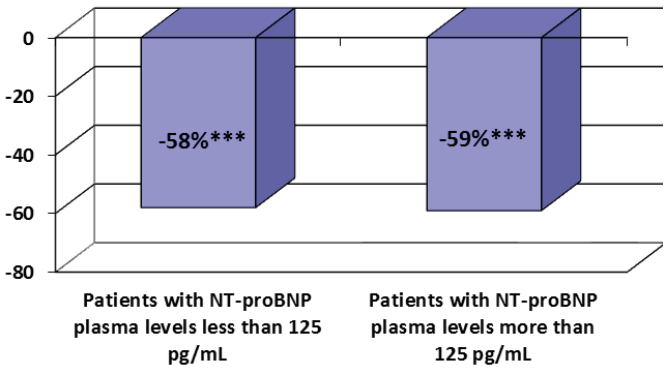

Figure 2. NT-proBNP plasma level dynamics under the influence of CpQ10-combined therapy in patients with NYHA class I-III

Association of the NT-proBNP plasma levels and the clinical, morphological, and functional features of CHF patients after the coenzyme Q10 treatment

According to the study design, patients started to receive CoQ10 therapy (60 mg/day) in addition to standard therapy for CHF after an initial CoQ10 plasma level evaluation. The use of CoQ10-combined therapy normalized the NT-proBNP plasma levels in both groups of patients (Figure 2).

Furthermore, CoQ10-combined therapy caused a significant increase in the average distance according to the 6-minute walk test (the average distance was slightly higher in patients with an initially increased NT-proBNP plasma level) and a non-significant LVEF increase (Table 6). An increase in CoQ10 plasma levels in both groups of patients was also observed (the dynamics were greater in patients with initially normal NT-proBNP plasma levels) (Table 6).

Association of the CoQ10 plasma levels and the clinical, morphological, and functional features of CHF patients after the coenzyme Q10 treatment

Some differences in the dynamics of the clinical, morphological, functional features, and laboratory test results in patients with different initial CoQ10 plasma levels were also observed. A significant reduction of the NT-proBNP plasma levels in both groups of patients was observed (the NT-proBNP plasma level was slightly higher in patients with initially higher CoQ10 plasma levels). There was evidence that the efficacy of CoQ10 therapy (Qudesan) was higher in patients with initially lower CoQ10 plasma levels (the dynamics of the 6-minute test results andas well as the LVEFs and CoQ10 plasma levels were greater in this group) (Table 7).

DISCUSSION

This prospective clinical study examined the relationships among the clinical, morphological, functional cardiac parameters, indicators of endothelial function, NT-proBNP plasma levels and CoQ10 concentration in patients with chronic heart failure of ischaemic aetiology.

According to this study, a wide range of CoQ10 concentrations was revealed: the CoQ10 plasma levels varied from 350 ng/mL to 1903 ng/mL and the average concentration was 826.3 (510.8; 1080.3) ng/mL. It was also shown that low levels of CoQ10 were associated with more severe heart failure and higher levels of NT-proBNP. Additionally, we revealed that high levels of NT-proBNP were associated with low exercise tolerance, reduced LVEF and a decrease in CoQ10 plasma levels.

Table 6. CoQ10-combined therapy (Qudesan) clinical, morphological, and functional features in patients with different NT-proBNP plasma levels

	Patients with NT-proBNP plasma levels less than 125 pg/mL (n=15)	Patients with NT-proBNP plasma levels more than 125 pg/mL (n=60)	*p*
Average NT-proBNP plasma level, pg/mL			
Before therapy	62.2 (49.8; 104.4)	264.2 (177.4; 491.9)	*0.001*
After 12 weeks	26.4 (13.6; 42.8)	108.20 (59.9; 155.8)	*0.001*
D%; p	-58; 0.005	-59; 0.001	
Average distance according to the 6-minute walk test, m			
Before therapy	405.0 (393.0; 427.0)	336.5 (300.8; 408.0)	*0.079*
After 12 weeks	457.0 (432.0; 520.0)	398.5 (351.3; 512.0)	*0.085*
D%; p	+12.8; 0.003	+18.4; 0.002	
LVEF, %			
Before therapy	43.0 (39.8; 44.0)	39.0 (36.5; 42.0)	*0.001*
After 12 weeks	46.0 (43.5; 49.0)	41.5 (39.5; 43.0)	*0.028*
D%; p	+6.9; 0.416	+6.4; 0.752	
Average CoQ10 plasma level, ng/mL			
Before therapy	1020.0 (744.4; 1217.0)	837.3 (510.8; 1080.3)	*0.228*
After 12 weeks	2310.0 (1160.0; 3415.0)	1000.0 (752.8; 1905.0)	*0.063*
D%; p	+126.5; 0.021	+19.4; 0.208	

Table 7. Changes in the CoQ10 plasma levels depending on, the dynamics of the clinical, morphological, and functional features, NT-proBNP and CoQ10 plasma levels

	Patients with CoQ10 plasma levels less than 700 ng/mL (n=35)	Patients with CoQ10 plasma levels more than 700 ng/mL (n= 40)	*p*
Average NT-proBNP plasma level, pg/mL			
Before therapy	156.4 (121.2; 220.4)	105.7 (53.7; 240.7)	*0.221*
After 12 weeks	87.5 (34.6; 277.4)	43.5 (15.2; 78.2)	*0.386*
D%; p	*-44.1; 0.046*	*-58.8; 0.001*	
Average distance according to the 6-minute walk test, m			
Before therapy	336.5 (307.3; 387.5)	405.0 (340.5; 432.0)	*0.059*
After 12 weeks	395.0 (339.5; 479.0)	453.0 (404.5; 525.0)	*0.101*
D%; p	*+17.4; 0.028*	*+11.8; 0.001*	
LVEF, %			
Before therapy	38.5 (35.0; 41.5)	41.0 (38.0; 43.5)	*0.58*
After 12 weeks	44.0 (42.0; 46.0)	42.0 (39.0; 45.0)	*0.78*
D%; p	*+14.3; 0.144*	*+2.4; 0.609*	
Average CoQ10 plasma level, ng/mL			
Before therapy	513.1 (442.5; 619.5)	1042.0 (960.0; 1283.5)	*0.001*
After 12 weeks	965.5 (545.5; 2410.0)	1910.0 (1365.0; 2460.0)	*0.208*
D%; p	*+88.2; 0.144*	*+83.2; 0.016*	

The study results indicate that manifested by impaired endothelium-dependent vasodilatation, endothelial dysfunction is accompanied by a reduction in the CoQ10 plasma level in patients with CHF. Additionally, the lower the CoQ10 plasma level the more severe the endothelial dysfunction. Therefore, it is expected that a correction of the CoQ10 deficiency will be required. CoQ10 deficiency correction will improve the endothelial function, thus reducing the tissue hypoxia associated with CHF. Furthermore, other study results showed that a reduction of the CoQ10 concentration to less than 730 ng/mL, was a poor prognostic factor in CHF patients. It is argued that a low CoQ10 plasma level is an independent mortality risk factor in this group of patients (22-25). This study revealed that the optimal CoQ10 concentration for the prediction of mortality was 730 ng/mL. Multivariate analysis, in which the concentration of CoQ10 was compared with standard predictors of survival in CHF patients (age, sex, history of myocardial infarction, NT-proBNP concentration (terminal pro b-type natriuretic peptide)), and the glomerular filtration rate (with the modification of diet in renal disease) showed that CoQ10 was an independent predictor of survival in CHF patients (23-26).

The literature suggests that lower CoQ10 levels are associated with an increasing severity of HF symptoms. Additionally, the aforementioned evidence suggests that CoQ10 may be useful in patients with CHF by replenishing deficient levels, which may improve ATP synthesis and left ventricular function. The beneficial effects of coenzyme Q10 supplementation have been observed in several age-related diseases, including heart failure. The CoQ10 (coenzyme Q10) level is significantly decreased in patients with this disease, which correlates with the severity of clinical symptoms (30).

To clearly that that the CoQ10 levels are corrected with the severity of clinical symptoms, we used a 12-wk treatment of CoQ10 in patients with HF. Our experience with CoQ10 therapy in patients with class II-III NYHA provide us with hope of success. We previously determined the most effective dose for patients with CHF (24-28). The soluble form of the drug was used as the CoQ10 therapy (20 mL vials), 1 mL of which contains 30 mg of CoQ10 and 4.5 mg of Vitamin E. CHF patients received different doses of CoQ10: 60 mg (2 mL of Qudesan® solution), 90 mg (3 mL of Qudesan® solution), and 120 mg (4 mL of Qudesan® solution). After 4 weeks of treatment, it was found that regardless of the CoQ10 dose, there was more a 2-fold increase in the CoQ10 concentration in all patients with CHF. In accordance with the data, we determined that the optimal daily CoQ10 dose of combination therapy in patients with CHF was 60 mg per day.

Some foreign studies used much higher doses of CoQ10 (18), because the liposoluble form of the drug was used. Qudesan® solution is a solubilized form of CoQ10, the bioavailability of which is higher than the bioavailability of the liposoluble form by at least 2.6 times. Therefore, a dose of 60 mg of water-soluble (solubilized form) CoQ10 should be approximately equal to 150-200 mg of liposoluble CoQ10.

It was found that treatment with CoQ10 led to more significant dynamics of the clinical, morphological, and functional parameters (the dynamics of the average distance according to the 6-minute walk test, LVEFs, and CoQ10 plasma levels) in patients with initially lower levels of CoQ10. We also also showed that the addition of CoQ10 to standard therapy for CHF patients with initially high NT-proBNP concentrations and reduced CoQ10 concentrations led to a significant decrease in the NT-proBNP plasma levels, increase in the CoQ10 concentrations, in-

crease in exercise tolerance and improvement of endothelial function.

There have been numerous observational reports over the last few decades reporting the usefulness of CoQ10 for improving HF symptoms, including the ejection fraction, left ventricular size and quality of life. However, these studies had several design shortcomings that prevented their translation into clinical practice (18, 31).

Our findings on the effect of CoQ10 in CHF combination therapy on the BNP and CoQ10 plasma levels are consistent with those of other authors. Tokareva et al. showed that long-term use of CoQ10 prevented the progression of chronic heart failure in patients with impaired myocardial contractility and original BNP levels in the normal range (less than 100 pg/mL) (29). In another analysis by Sander et al., with CoQ10 doses ranging from 60–200 mg/day, it was shown that there was a 3.7% net improvement in the ejection fraction (1.59 to 5.77; p<0.00001) (17).

Fotino et al. reported similar results in a meta-analysis; CoQ10 supplementation resulted in a pooled mean net increase in the ejection fraction of 3.67%, further suggesting the benefits of CoQ10 therapy (32).

The largest randomized trial performed to date (completed in 1993 and enrolled 641 patients) demonstrated that compared with placebo, CoQ10 reduced the risk of HF hospitalization (73 versus 118, $p<0.001$) and complications of HF, such as pulmonary oedema and cardiac asthma (20 versus 51 and 97 versus 198, $p<0.001$), and our results are in accordance with these findings (33).

Coenzyme Q10 potentially enhances cardiac function, probably through a variety of mechanisms. CoQ10 plays a critical role in ATP generation by accepting electrons from complexes I and II and transporting them to complex III, and at which point they are ready to be reduced by complexes I and II again. This electron transportation allows hydrogen ions (H^+) to be pumped across the inner mitochondrial membrane (IMM), which drives the synthesis of ATP via ATP synthase. CoQ10 has been shown to inhibit the peroxidation of cell membrane lipids and reduce the oxidation of circulating lipolipids. In addition to its antioxidant activity, CoQ10 also seems to improve endothelial function (34, 35).

CONCLUSION

In HF patients, CoQ10 supplementation induced improvements in functional cardiac parameters, such as the ejection fraction. Our results suggest that al CoQ10 supplementation may be a useful option for effective management of heart failure and warrant future adequately powered randomized controlled trials of CoQ10 supplementation in patients with HF.

Conflict Of Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

Acknowledgements

The determination of CoQ10 plasma levels and the writing of the article were supported by Grant of Russian Science Foundation No. 14-15-00126.

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