

Coenzyme Q10 Regulates Gene expression of Myocardial Infarction in Isoproterenol Model

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Abstract

Cardiac remodeling is defined by changes in the genome's expression, as well as molecular, cellular, and interstitial state alterations, all of which lead to changes in the heart's function. Coenzyme Q10 (CoQ10) is increasingly the most critical component of mitochondria's electron transport chain, which is required for ATP generation. The main intent of this scrutiny is to assess CoQ10's role in myocardial infarction (MI) in male rats. The rats were split into four factions: the controls (C), the CoQ10 treated batch, ISO treated batch and CoQ10+ISO treated batch. Biochemical markers of liver functions (AST, ALT, ALP, albumin, and total protein), cardiac markers, electrolytes, TNF, oxidative stress [malondialdehyde (MDA)], and antioxidative [superoxide dismutase (SOD), and reduced glutathione (GSH)] were all examined. qPCR was used to assess the cardiac tissues expression of the the angiogenesis-related gene vascular endothelial growth factor (VEGF), the migration-related gene matrix metalloproteinase 9 (MMP9), and the antioxidant-related gene Heme Oxygenase-1 (HO-1). CoQ10 treatment of ISO-bearing rats reduced hepatic damage as shown by restored liver function measures, reduced cardiac MDA levels, increased cardiac GSH and SOD levels, upregulated expression of VEGF, MMP9, and HO-1. It's concluded that CoQ10 played a preventive function against heart injury generated by the ISO model based on these findings.

Keywords: Gene expression, CoQ10, Oxidative stress, VEGF, MMP9, HO-1

INTRODUCTION

Worldwide, cardiovascular diseases (CVDs) proceeds being the leading cause of death [1]. Acute myocardial infarction (MI) induced by the obstruction of a coronary artery is a primary cause of morbidity and mortality in humans [2]. Angina pectoris (deep pain) is a symptom of MI, which is commonly accompanied by nausea, shortness of breath, ischemia, and dizziness [3]. After an ischemia episode, inflammation plays a vital role in causing cardiac tissue damage. Neutrophils penetrate the infarcted area, where they release proteolytic enzymes and produce reactive oxygen species, which can cause cardiac cell injury [4].

Cardiac remodeling is defined by changes in the genome's expression, as well as molecular, cellular, and interstitial state alterations, all of which lead to changes in the heart's function [5]. The isoproterenol (ISO) induced MI model is one of the most extensively used experimental models for studying the therapeutic effects of a variety of medications on heart function. ISO which imitates the activation of the adrenergic receptor, may cause myocardial necrosis when given subcutaneously [6]. Some of the fundamental procedures of myocardial remodeling in the heart include oxidative stress and inflammatory responses [7]. By activating matrix metalloproteinase, excessive generation of volatile species of oxygen and inflammatory cytokines can lead to changes in the external cellular matrix (MMP) [8].

In the ISO-treated Model, numerous natural items and dietary complements with antioxidant potential displayed ROS hunting. Coenzyme Q10 (CoQ10) is one of the antioxidants generated in the human body and the first medicine to reduce heart mortality by half in all cases. CoQ10 is a fundamental component of the biochemical mechanism that provides energy to cells. It can also help to reduce the ischemia and reperfusion injury associated with coronary revascularization [9]. Co-Q10 is accountable for intracellular energy production, the alleviation of endothelial dysfunction, and the activation of mitochondrial uncoupling proteins [10].

In return, this research aims to investigate the effects of Q10 medication on myocardial infarction caused by ISO dosages.

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And look at biochemical markers, genetic alterations, and biochemical changes to see how effective it is.

MATERIALS AND METHODS

Animals

According to the institutional animal care and use committee, study ethics approval was received from the research ethical committee (2021/021AO), Faculty of Medicine, Umm Alqura University, Saudi Arabia. ARRIVE guidelines were followed in the execution of all techniques. Male rats weighing 115–125 g were used in the study. The rats were kept in a uniform temperature-controlled facility with a 24-hour cycle and were fed normal food and water *ad libitum*.

Myocardial Infarction Induction

Subcutaneous injection of 150 mg/kg ISO dissolved in saline once daily for two consecutive days caused myocardial infarction in rats through dose based on published literature [11].

Experimental Design

The following groups of infarcted rats were separated at random into six animals each.

1. *The control group (C)*: Throughout the trial, the rats were fed a standard laboratory rat diet.
2. *CoQ10 group (CoQ10)*: The rats were given Q10 (10mg/kg b.w.) via oral gavage every day.
3. *Isoproterenol group (ISO)*: The rats were fed a standard rat diet and subcutaneously (SC) injected with isoproterenol (ISO) at a dose of (150 mg/kg in 2ml saline solution) for two consecutive days.
4. *CoQ10 + ISO group*: The rats were given (10mg/kg b.w.) of Coenzyme Q10 via oral gavage for 2 weeks before receiving isoproterenol (ISO) at a dose of (150mg/kg b.w in 2ml saline, S.C) for two consecutive days.

Blood Sampling

Blood samples were collected in centrifuge-safe glass tubes, allowed to clot, and then centrifuged for 15 minutes at 4000 rpm. The clear, non-hemolyzed sera were rapidly extracted and placed in labeled Eppendorf tubes; the sera were then frozen at -20°C for various biochemical analyses. After exsanguination, the heart was immediately removed, and homogenized for biochemical assay or frozen at -80°C (RNA extraction).

Assessment of Biochemical Parameters

Biochemical parameters are evaluated. Using commercially available kits, the amount of serum from liver enzymes [aspartate transaminase (AST), alanine transaminase (ALT)], albumin, and total proteins were determined (Roche Diagnostics, Saudi Arabia). Cardiac markers, TNF, and serum electrolytes were also assessed. Glutathione (GSH) and superoxide dismutase (SOD) experienced a reduction due to the antioxidant markers. The lipid peroxidation marker malondialdehyde (MDA) was assessed in tissues using kits attained from Roche Diagnostics.

Assessment of Genetic Variations in Cardiac Samples

Relative expression of the VEGF, MMP9, and HO-1 gene variations in cardiac specimens from all groups, were determined using real-time PCR. Total RNA was extracted initially, and subsequently reverse transcribed into cDNA using kits from Thermo Scientific (#L0852 and #EL0331, respectively).

The sequences of primers were as follows: F: 5' CACATCCAGACAGACACCAGT 3' and R: 5' CTACAAATGGGAATGTCTCTGC 3' for HO-1; F: 5' TCGAAGGCGACCTCAAGTG 3' and R: 5' TTCGGTGTAGCTTTG GATCCA 3' for MMP9; F: 5' GATCATGCGGATCAAACCTCACC 3' and R: 5' CCTCCGGACCCAAAGTGCTC 3' for VEGF; F: 5' CATGGATGACGATATCGCT 3' and R: 5' CATGAGGTAGTCTGTCAGGT 3' for β actin (internal control).

Analytical Statistics

The data were analyzed with GraphPad Prism 5.0. The outcomes of the experiments were conveyed as mean standard error mean (SEM). To gauge the data, the One-way analysis of variance (ANOVA) was adopted, after that the Tukey test for variable comparisons. The statistical significance was determined by P 0.05.

RESULTS AND DISCUSSION

Effect of Coenzyme Q10 on Liver Function Tests

In comparison to control rats, ISO-treated rats significantly increased the activity of the ALT, AST, Alb, and ALP enzymes **Table 1**. The activities of ALP, AST, and ALT were all dramatically reduced after taking CoQ10. Furthermore, in a group of CoQ10+ISO, a slight shift in Alb and TP activity was observed.

Table 1. Liver functions in ISO treated rats after treatment with CoQ10

Groups	Control N=6	CoQ10 N=6	ISO N=6	CoQ10+ISO N=6
ALT, U/L, mean±SEM	12.52±0.22 ^a	13.81±0.20 ^a	49.210±0.62 ^b	36.79±1.15 ^c
AST, U/L, mean±SEM	44.65±0.34 ^a	45.89±0.52 ^a	81.77±0.66 ^b	44.61±1.26 ^c
Albumin, g/dl, mean±SEM	3.98±0.25 ^a	3.88±0.21 ^a	2.52±0.06 ^b	3.13±0.15 ^c

ALP, mg/dl, mean±SEM	143.65±0.13 ^a	145.6±0.21 ^a	281.13±1.52 ^b	234.67±12.5 ^c
TP, g/dL mean±SEM	4.73±0.17 ^a	4.98±0.21 ^a	3.31±0.21 ^b	3.81±0.13 ^c

Data are expressed by means ± SEM. Small (a-c) letters show the marked change at P ≤ 0.05. The same letters show (non-significant) and the significant are expressed by dissimilar letters.

Cardiac Indicators and Serum Electrolytes in ISO-Treated Rats after Therapy with Coenzyme Q10

In comparison to control rats, ISO-treated rats had significantly increased CK-MB activity (P<0.05). When compared to the CoQ10+ISO group of ISO-treated rats, CoQ10 administration dramatically reduced CK-MB activity

in ISO-given animals **Table 2**. In addition, LDH and CK showed similar findings. According to TNF, the effect of administering Q10 with ISO reduced the activity of TNF compared to the CoQ10+ISO group in terms of the rest of the parameters. In a group of CoQ10+ISO treated rats, the CoQ10 treatment dramatically reduced the amount of K and Na content in the serum.

Table 2. The effects of CoQ10 on cardiac indicators, serum electrolytes, and TNF

Groups	Control N=6	CoQ10 N=6	ISO N=6	CoQ10+ISO N=6
LDH, U/L, mean±SEM	198.12±4.13 ^a	204.23±4.23 ^a	492.65±2.24 ^b	220.12±3.22 ^c
K, mmol/L, mean±SEM	3.56 ±0.72 ^a	3.99±0.22 ^a	8.96±2.04 ^b	6.21±1.22 ^c
Na, mmol/L, mean±SEM	139.52±1.05 ^a	135.98±0.96 ^a	159.41±2.56 ^b	144.90±0.87 ^c
CK-MB, IU/L, mean±SEM	12.99±0.75 ^a	15.02±0.62 ^a	24.85±0.45 ^b	14.82±0.21 ^c
CK, U/L, mean±SEM	141.13±0.62 ^a	143.02±0.60 ^a	235.23±1.89 ^b	148.54±2.91 ^c
TNF, pg./ml, mean±SEM	5.01±0.91 ^a	4.92±0.88 ^a	9.14±0.12 ^b	5.96±0.23 ^c

Data are expressed by means ± SEM. Small (a-c) letters show the marked change at P ≤ 0.05. The same letters show (non-significant) and the significant are expressed by dissimilar letters.

Effect of Coq10 on Oxidative and Antioxidative Markers

Untreated ISO-bearing rats show significantly higher cardiac levels of the lipid peroxidation marker MDA and

significantly lower cardiac levels of antioxidant indicators (GSH and SOD) than the other control group **Table 3**. These indicators were restored to levels similar to those in the control groups after treatment with CoQ10.

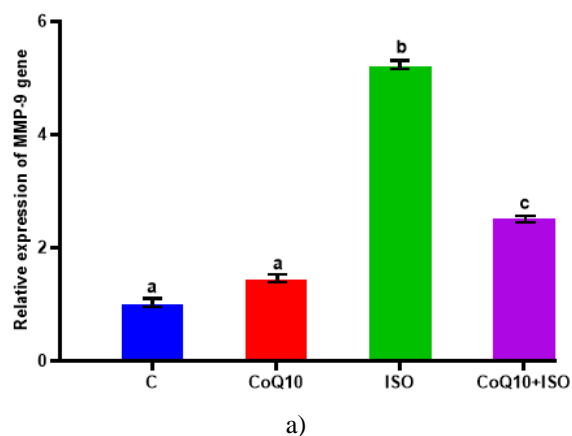
Table 3. The effects of CoQ10 on oxidative and antioxidative markers

Groups	MDA (nmol/ g tissue)	GSH (nmol/ g tissue)	SOD (U/ g tissue)
Control	367.63±0.43 ^a	4.31±0.26 ^a	59.63±1.34 ^a
CoQ10	367.86±0.44 ^a	4.22±0.33 ^a	61.09±1.75 ^a
ISO	519.77±0.26 ^b	2.06±0.29 ^b	50.28±1.81 ^a
CoQ10+ISO	382.7±8.91 ^c	5.13±0.38 ^c	57.21±2.12 ^a

Data are expressed by means ± SEM. Small (a-c) letters show the marked change at P ≤ 0.05. The same letters show (non-significant) and the significant are expressed by dissimilar letters.

Effect of CoQ10 on the Expression of VEGF, MMP-9, and HO-1 genes

When qPCR data were compared to control groups, the ISO-bearing rats had a significantly higher cardiac expression of HO-1, MMP9, and VEGF **Figure 1**. The expression of these genes was restored to levels comparable to the control groups after administration of CoQ10.



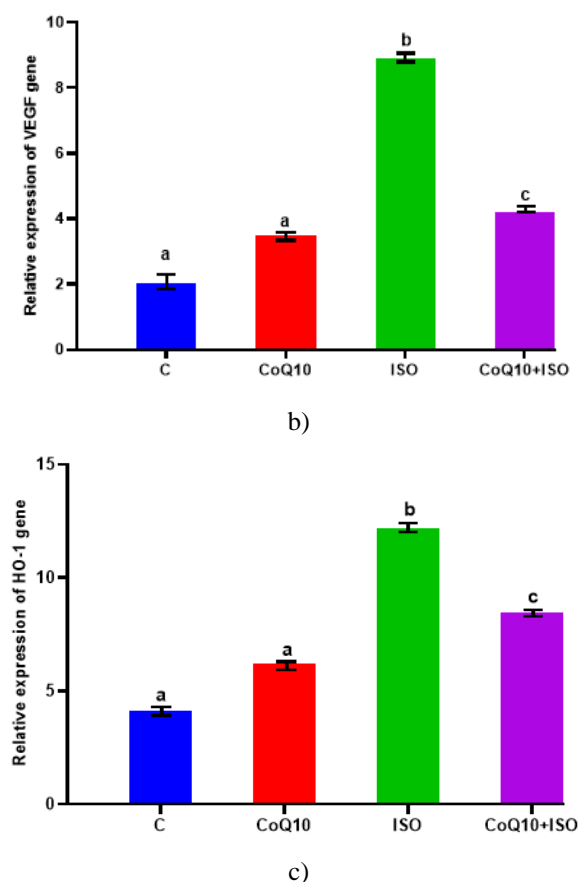


Figure 1. Real-time PCR detection of variations in VEGF, MMP9, and HO-1 gene expression in cardiac tissues of dissimilar groups. As an internal control, β -actin was used. Fold changes imply that Mean \pm SEM was used to represent the expression. Small (a-c) letters show the marked change at $P \leq 0.05$. The same letters show (non-significant) and the significant are expressed by dissimilar letters.

A key cause of unfavorable cardiac remodeling is reformed inflammatory mediator expression and cells' failure to retort to growth factors [12]. The goal of this study was to demonstrate the potential preventive and curative effects of CoQ10 on the toxicity of ISO on cardiac injury and blood parameters. CoQ10, on the other hand, maybe a therapeutic option for people suffering from heart disease. According to some evidence, CoQ10 plays an important role in ATP synthesis, is a potent anti-inflammatory agent, and may help endothelial function [13].

ISO was given subcutaneously to rats to cause cardiac remodeling. Catecholamine has a positive inotropic effect that helps the heart operate at low levels [14]. However, excessive doses of isoproterenol deplete the heart's energy supply, resulting in biochemical and structural alterations in cardiomyocytes [15]. In this study, the rats' group given ISO had a significant increase in serum of liver ALT, AST, and ALP, as well as a significant decrease in serum albumin and total protein. These findings are consistent with Barman *et al.*

[16]. The increased levels of ALT, AST, and ALP could be due to ISO's cytotoxic effect, which caused injury to liver cells and canaliculi, as well as the discharge of these enzymes, which resulted in their elevation in the liver and bloodstream; since ALT and AST are found in the cytoplasm of hepatocytes [17].

In line with Omnia *et al.* findings, they found that inducing rats with ISO resulted in a considerable reduction in Alb and TP levels as opposed to the control group [18]. The reduction in proteins demonstrates the degenerative consequence of ISO on hepatic cells since Alb and TP are hands of the biosynthetic liver role or an increase in the dispossession of the degree of protein consumption [19].

Furthermore, when ISO dissociates to the Na ion, ammonium ions are produced, which can induce cardiac damage [20]. Increased quantities of ammonium ions (NH_4^+) cause damage to heart tissues, which raises serum cardiac enzyme levels. As a result, the increase in these enzymes may have been halted due to the injury and oxidative stress generated by ISO on the heart, where a large number of cytosolic cardiac enzymes flowed into the blood [21].

Creatine kinase-MB (CK-MB) and Creatine Kinase (CK) are superior and unique markers that can indicate myocardial necrosis [22]. In the serum of rats, the rise of CK-MB and CK activity as a result of ISO therapy is evident. Management with CoQ10 prevented the increase in CK-MB and CK activity in serum in this investigation. CoQ10 can diminish CK-MB activity in ISO-induced cardiotoxicity and cardiac hypertrophy in male rats, according to previous research [9, 23, 24].

The content of malondialdehyde (MDA, a lipid peroxidation product) in ISO-treated rats was reduced by treatment of CoQ10. It was known that, in myocardial necrosis, the lipid peroxidation is a key pathogenic process and the buildup of lipid hydroperoxides in the heart injury. By treatment with CoQ10, it worked as scavenging or neutralizing the free radicals, inhibiting hydrogen peroxide and tumor necrosis factor, inhibiting xanthine oxide, interfering with the oxidative cascade and preventing the outcome of lipid peroxidation [25], in addition, CoQ10 act as an oxygen quenching and making it less available for oxidative reactions, and inhibition of cytochrome P450 in case of oxidative stress conditions [26].

In this investigation, GSH and SOD levels in the heart of ISO-treated rats were shown to be significantly lower than in the control group. The GSH level was greatly restored after therapy with CoQ10. Temporarily, the observed fall in GSH and SOD content could be due to the glutathione reductase enzyme converting most GSH in the liver to GSSG to protect liver cells from harmful resources [27]. The reduction in SOD activity is caused by an increase in the production of oxygen radicals that are reactive such as hydrogen peroxide and superoxide that inhibit these enzymes [28]. Treatment with

CoQ10 boosts SOD activity, scavenges superoxide radicals, and decreases free radical-induced cardiac damage [29].

Next, the anti-inflammatory effect of CoQ10 against ISO induction was evidenced by the profound upregulation of VEGF. Another important finding is that CoQ10 triggered the antioxidant genes, HO-1 and MMP-9. HO-1 is a rate-limiting enzyme that controls oxidative and inflammatory processes that occur often in ISO-induced nephrotoxicity. According to Khodir *et al.*, (2017), CoQ10's antioxidant, anti-inflammatory, and anti-apoptotic characteristics are brought about by its influence on the Nrf2/HO-1 pathway [30]. According to Pala *et al.*, (2016), CoQ10's cytoprotective action is due to the modification of the expression of HO-1, demonstrating CoQ10's anti-inflammatory properties and underlining its function in antioxidant defenses [31].

In fact, ROS is one of the crucial antecedents of MMP and VEGF regulation and expression. Furthermore, CoQ10 is an effective antioxidant against ROS, inhibiting the production of cytokines and MMP [32]. As a result, CoQ10's modulatory effect on MMP-9 and VEGF levels in this research might be attributed to its interaction with ROS mediators [33].

CONCLUSION

This study found that administering rats CoQ10 decreases cardiac inflammation, and protects against heart damage caused by the ISO model. CoQ10 treatment improved liver, cardiac, and gene expression, which might be linked to the reduction in stress due to oxidation and antioxidant defense restoration in tissues.

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