Pharmacology & Therapeutics 124 (2009) 259–268

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: I. Kimura

Role of coenzyme Q10 (CoQ10) in cardiac disease, hypertension and Meniere-like syndrome

Adarsh Kumar [a,*], Harharpreet Kaur [b], Pushpa Devi [c], Varun Mohan [b]

[a] Cardiology Deptt, Govt. Medical College/GND Hospital, Amritsar, Punjab, Amritsar, Punjab, India
[b] Medicine Deptt, Govt. Medical College/GND Hospital, Amritsar, Punjab, Amritsar, Punjab, India
[c] Microbiology Deptt, Govt. Medical College/GND Hospital, Amritsar, Punjab, Amritsar, Punjab, India

ARTICLE INFO

Keywords:
Coenzyme Q10
Bioenergetics
Antioxidant
Heart disease
Hypertension
Meniere's disease

ABSTRACT

Coenzyme Q10 (ubiquinone) is a mitochondrial coenzyme which is essential for the production of ATP. Being at the core of cellular energy processes it assumes importance in cells with high energy requirements like the cardiac cells which are extremely sensitive to CoQ10 deficiency produced by cardiac diseases. CoQ10 has thus a potential role for prevention and treatment of heart ailments by improving cellular bioenergetics. In addition it has an antioxidant, a free radical scavenging and a vasodilator effect which may be helpful in these conditions. It inhibits LDL oxidation and thus the progression of atherosclerosis. It decreases proinflammatory cytokines and decreases blood viscosity which is helpful in patients of heart failure and coronary artery disease. It also improves ischemia and reperfusion injury of coronary revascularisation. Significant improvement has been observed in clinical and hemodynamic parameters and in exercise tolerance in patients given adjunctive CoQ10 in doses from 60 to 200 mg daily in the various trials conducted in patients of heart failure, hypertension, ischemic heart disease and other cardiac illnesses. Recently it has been found to be an independent predictor of mortality in congestive heart failure. It has also been found to be helpful in vertigo and Meniere-like syndrome by improving the immune system. Further research is going on to establish firmly its role in the therapy of cardiovascular diseases.

Contents

Abbreviations: CoQ10, Coenzyme Q10; CHF, Congestive heart failure; DCM, Dilated cardiomyopathy; HCM, Hypertrophic cardiomyopathy; ecSOD, Extracellular superoxide dismutase; CAD, Coronary artery disease; AMI, Acute myocardial infarction; EF, Ejection fraction; NYHA, New York Heart Association.

* Corresponding author. 17 F Beauty Avenue, Phase 2 Amritsar, Punjab, India. Tel.: +91 1832500707, 9915578231 (mobile).
E-mail address: adarshkumar_27@yahoo.com (A. Kumar).

0163-7258/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2009.07.003

1. Introduction

Advances in molecular medicine have provided novel insights into the pathophysiology of heart disease. Coenzyme Q10 (CoQ10) exerts action at the cellular level and rectifies some of the basic deficiencies leading to aggravation of these diseases. These include correction of the energy depletion and oxidant stress which are inherent in these conditions.

Coenzyme Q10 plays a key role in mitochondrial oxidative phosphorylation and ATP production. It is therefore essential for all energy-dependent processes in the heart, including heart-muscle contraction and functioning of ATP regulated membrane channels. Heart is a metabolically active organ which needs plenty of energy and has a large number of mitochondria. CoQ10 is found in the membranes of many organelles. Since its primary function in cells is in generating energy, the highest concentration is found on the inner membrane of the mitochondrion. Some other organelles that contain CoQ10 include endoplasmic reticulum, peroxisomes, lysosomes and vesicles. It is a membrane stabilizer and preserves myocardial sodium–potassium ATPase activity and stabilizes myocardial calcium-dependent ion channels.

Heart is highly sensitive to CoQ10 deficiency. Both dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are frequently accompanied by defective levels of specific oxidative phosphorylation/respiratory enzyme activities. (Rustin et al., 1994; Marin-Garcia et al., 1995). The reduced energy reserve in heart failure may be considered to contribute to the progression of the disease (Vogt, 1998). Exogenous CoQ10 is taken up by CoQ10-deficient cells and can be demonstrated to be incorporated into the mitochondria for maintenance of optimal cellular and mitochondrial function. (Nakamura et al., 1980) Newer P31 NMR spectroscopy studies have documented enhanced cellular high energy phosphate concentrations with CoQ10 supplementation in experimental models (Crestanello et al., 1996). CoQ10 thus has potential for prevention and treatment of cardiovascular disease by improving cellular bioenergetics.

2. Chemistry

Coenzyme Q10 was first isolated in 1957 from beef mitochondria and is known to be highly concentrated in heart-muscle cells due to the high energy requirements of this cell type (Crane et al., 1957). It is a naturally occurring fat-soluble vitamin-like quinone commonly known as, CoQ10. It is also called ubiquinone as it is ubiquitous or present in all eukaryotic cells. Chemically CoQ10 is 2, 3 dimethoxy–5 methyl–6 decaprenyl benzoquinone. The functional group in CoQ10 is the quinone ring. By reduction of the quinone to quinol (H2 CoQ10) a carrier of protons and electrons is produced.

3. Sources

It is present in foods such as beef, poultry and broccoli (Ellin et al., 1999). Other sources of CoQ10 are soya oil, fish oils, peanuts, sardines and mackerel. Dietary intake of CoQ10 is 2–5 mg/day, which is always inadequate to provide levels in the body required to be beneficial in pathological states.

4. Potential clinical uses for Coenzyme Q10

CoQ10 is useful in arteriosclerosis, ischemic heart disease, chronic heart failure (for both systolic and diastolic heart failure), hypertrophic cardiomyopathy, cardiovascular surgery, hypertension, arrhythmias, valvular heart diseases, toxin-induced cardiomyopathy including statin cardiomyopathy and Meniere's disease.

5. Coenzyme Q10 deficiency in cardiac diseases

Studies performed by Folkers et al. (1970) showed that 70–75% of heart patients exhibit low levels of CoQ10. Circulating levels of CoQ10 were significantly lower in patients with ischemic heart disease and in those with dilated cardiomyopathy as compared to healthy controls (Langsjoen, 1990). Myocardial deficiencies of CoQ10 were also found in the majority of patients with aortic stenosis or insufficiency, mitral stenosis or insufficiency, diabetic cardiomyopathy, tetralogy of Fallot, atrial septal defects and ventricular septal defects (Folkers et al., 1970). The concentrations of CoQ10 declined progressively in both blood and myocardial tissue with increasing severity of heart disease (Littarru et al., 1972).

Normal blood levels range from 0.7 to 1.0 μg/mL (Redalieu et al., 1968). Doses of 30–60 mg/day (~ 1 kg of body weight) are generally recommended to prevent CoQ10 deficiency and to maintain normal serum concentrations. However optimum clinical benefit requires above normal CoQ10 blood levels which may be 2 to 4 times higher. High blood levels may be required to attain an elevation of tissue CoQ10 levels or to rescue defective mitochondrial function. Therapeutic doses of 100–200 mg/day are advocated for the treatment of chronic heart diseases. In patients with cardiomyopathy and myocardial deficiency of CoQ10, oral administration of 100 mg/day of CoQ10 for 2–8 months resulted in an increase in myocardial CoQ10 levels ranging from 20 to 85% (Folkers et al., 1985). These higher doses may achieve serum concentrations of 2.0–3.0 μg/mL, reported by some investigators to have a positive impact on cardiovascular health. Patients with advanced heart failure often fail to achieve adequate blood (plasma) levels, even when high doses of conventional CoQ10 are given. It has recently been shown that significant clinical benefit in heart failure patients requires a plasma CoQ10 level of around 4 μg/mL (Langsjoen, 2007).

In severe heart failure patients, the only way these higher levels can be obtained appears to be with ubiquinol, the reduced form which is much more effective than conventional ubiquinone since it is eight times better absorbed. Most of commercially available CoQ10 supplements comprise ubiquinone. The most advanced CoQ10 formulas now contain ubiquinol (Hosoe et al., 2007). Recommended daily dosages of ubiquinol range from 100 mg to 300 mg. In a dose of 450 mg a day it achieved a plasma level of 4 μg/mL and was much more successful in reversing the course of a severe heart failure. In the recent study conducted by Dr. Langsjoen, the ejection fraction improved from 24% up to 45% in ubiquinol-treated patients who had follow up echocardiograms. This represented a recovery of up to 88% in this critical measurement of cardiac output. The higher blood levels of CoQ10 and the improved ejection fractions were accompanied by a remarkable clinical improvement in these heart failure patients. It is believed that supplemental ubiquinol represents a major scientific advance in the fifty-year history of CoQ10 research (Langsjoen, 2007). CoQ10 dosage guidelines, which appeared to be safe and well tolerated were recently suggested for adults to be up to 1200 mg/day (Hathcock & Shao, 2006).There is a delay in the onset of clinical improvement of 1 to 4 weeks after initiation of treatment and a further delay of several months in maximal clinical benefit. Possible reasons for this delay include time to attain adequate tissue levels of CoQ10 or time to synthesize CoQ10 dependent apoenzymes.

6. Mechanism of action

The possible therapeutic mechanisms of action of coenzyme Q10 in cardiovascular diseases are as follows:

Improvement of cardiac bioenergetics
Direct free radical scavenger and antioxidant effect
Correction of coenzyme Q10 deficiency state
Improved endothelial function and vasodilatory effect

Direct membrane-stabilizing activity due to phospholipid–protein interactions
Preservation of myocardial Na^+–K^+ ATPase activity
Stabilization of integrity of Ca2+-dependent slow channels
Correction of mitochondrial "leak" of electrons during oxidative respiration
Induction of DT diaphorase
Possible effects on prostaglandin metabolism
Antiviscosity effect
Altering the immune response
(Greenberg & Frishman, 1990).

6.1. Improvement of cardiac bioenergetics

Cardiac contraction occurs after Ca2+ release from sarcoplasmic reticulum (SR) which activates the contractile proteins. During diastole, cytosolic Ca2+ re-sequesters into the SR. The cardiac contraction and the uptake of free cytoplasmic calcium into the sarcoplasmic reticulum is an energy-requiring mechanism (Kayo & Carsten, 2005). Myocardial relaxation which is dependent on active Ca2+ uptake by the sarcoplasmic reticulum is not a passive process. Rather this latter step requires more energy. In cardiac failure, changes in Ca2+ transport and metabolism have also been found (Marin-Garcia et al., 2001). Myocardial failure may be related to decreased energy production by the mitochondria. There is a decrease in energy availability for Ca2+ uptake in SR (diastolic failure) and for delivery to the contractile apparatus impairing cross bridge cycling (systolic failure).Since CoQ10 participates in the transport of electrons from organic substrates to oxygen in the respiratory chain of mitochondria with the production of energy, it has a role in providing energy for the functioning of the failing and energy depleted heart.

6.2. Antioxidant action

Because of its ability to transfer electrons it acts as an antioxidant. The presence of CoQ10 in other membranes besides mitochondria, shows that its antioxidant effect may also be of physiological importance. In most membranes enzymes have been defined which can reduce the quinone and oxidize the quinol (Crane, 2001).CoQ10 must be reduced to ubiquinol denoted QH2 to wield its maximum anti-oxidative function. In its reduced form (ubiquinol), the coenzyme Q10 molecule holds electrons loosely and will quite easily give up one or two electrons to neutralize free radicals. It is this form which displays its strongest antioxidant activity (Mellors & Tappel, 1966). Sophisticated biochemical markers of oxidative injury are now demonstrating in-vivo the antioxidant cell protective effects of CoQ10. Its main role as an antioxidant is in the mitochondria where it first participates in the process by which free radicals are generated and then helps to quench the extra free radicals that threaten cellular components such as DNA, RNA, and cell membranes.

Its antioxidant properties contribute to prevention of lipid peroxidation. It has been found to be efficient in preventing LDL oxidation which is an important step in evolution of atherosclerosis (Yokoyama et al., 1996).CoQ10 has a direct anti-atherogenic effect, which has been demonstrated in apolipoprotein E-deficient mice fed with a high-fat diet. In this model, supplementation with CoQ10 at pharmacological doses was capable of decreasing the absolute concentration of lipid hydroperoxides in atherosclerotic lesions and of minimizing the size of atherosclerotic lesions in the whole aorta. Whether these protective effects are only due to the antioxidant properties of coenzyme Q or due to some other mechanisms remains to be established (Littarru & Tiano, 2007).

6.3. Endothelial function

Endothelium-bound extracellular Superoxide Dismutase (ecSOD) activity is a major antioxidant enzyme system of the vessel wall which is reduced in patients with coronary artery disease. A recent study showed improvement in the endothelial relaxation with coenzyme Q10 administration. This might be related to its capability of enhancing endothelial function by counteracting nitric oxide oxidation. (Tiano et al., 2007; Belardinelli et al., 2008). CoQ10 has been recently shown to improve the endothelial relaxation in diabetic patients Indeed, in vitro study indicates that CoQ10 can efficiently prevent high glucose induced endothelial cell apoptosis and adhesion to monocytes, which are relevant to the pathogenesis of atherosclerosis (Tsuneki et al., 2007).

6.4. Membrane stabilization and fluidity

The membrane-stabilizing property of CoQ10 has been postulated to involve the phospholipid–protein interaction that increases prostaglandin (especially prostacyclin) metabolism. It is thought that CoQ10 stabilizes myocardial calcium-dependent ion channels and prevents the depletion of metabolites essential for ATP synthesis. CoQ10 also decreases blood viscosity and improves blood flow to cardiac muscle in patients with ischemic heart disease (Kato & Yoneda, 1990).

6.5. Reduction in proinflammatory cytokines

It is becoming increasingly apparent that inflammatory mediators play a crucial role in the development of congestive heart failure and acute myocardial infarction and several strategies to counterbalance the different aspects of inflammatory response are considered. The most important proinflammatory cytokines implicated in the progression of congestive heart failure are IL-6 and TNF-alpha. A double-blind placebo-controlled randomized trial conducted on 31 patients of heart failure of mixed etiology for 12 weeks using 270 mg/day of ubiquinol along with oral carnitine showed marked reduction in IL-6 and TNF-alpha in the treated group as compared with the placebo. Thus CoQ10 also acts by altering the immune response (Kumar et al., 2007a,b).In a recent study the administration of CoQ10 significantly attenuated the increase of oxidative and nitrative stress markers and inflammatory markers in a dose-dependent manner. CoQ10 reduced the elevated serum insulin levels, although it did not affect the elevated glucose level and dyslipidemia. It also reduced elevated blood pressure, but did not affect body weight gain in cases of metabolic syndrome. In addition, CoQ10 improved endothelial dysfunction in the mesenteric arteries suggesting that the antioxidant properties of CoQ10 can be effective in ameliorating cardiovascular risk in metabolic syndrome (Masaru et al., 2008).

7. Role of Coenzyme Q10 in congestive heart failure (CHF)

Chronic heart failure represents a major public health burden and its prognosis is comparable to that of a malignant disease.

7.1. Deficiency in congestive heart failure

Heart failure is often characterized by an energy depletion status that has been associated with low endogenous CoQ10 levels. Its levels are depleted in both serum and myocardial tissue samples of patients with chronic heart failure (Folkers et al., 1970, 1985). The myocardial tissue levels in CHF patients are on average 33% lower than in control patients. Patients with severe CHF, namely New York Heart Association (NYHA) classes III and IV, tend to have lower levels of endogenous CoQ10 than that of patients with NYHA class I CHF or healthy subjects and may be more likely to attain a favourable clinical

response to CoQ10 supplementation (Mortensen et al., 1984). The need for measurement of plasma CoQ10 is based on the relationship between levels and outcomes, as in chronic heart failure, where it may identify individuals most likely to benefit from supplementation therapy. During CoQ10 supplementation plasma CoQ10 levels should be monitored to ensure efficacy, given that there is variable bioavailability between commercial formulations, and known inter-individual variation in CoQ10 absorption (Molyneux et al., 2008a,b).

Its deficiency may well be a primary etiologic factor in some types of heart-muscle dysfunction while in others it may be a secondary phenomenon. In both cases it is a treatable factor in this otherwise hopeless condition. The possible usefulness of the CoQ10 in the treatment of CHF may be related to its ability to increase ATP synthesis with enhancement of myocardial contractility (Crane, 2001). Recently it has been found to be an independent predictor of mortality in congestive heart failure (Molyneux et al., 2008a,b).

7.2. Oxidative stress

In addition, the myocardium of patients with heart failure demonstrates increased oxidative stress which can be corrected by CoQ10. With CoQ10 there was a significant decline in TBARS and MDA which are indicators of oxidative stress, indicating that scavenging of free radicals may be a possible mechanism for the beneficial effect of CoQ10 in heart failure (Kumar et al., 2002).

7.3. Trials relating to congestive heart failure

Improvement in myocardial function with CoQ10 supplementation has been demonstrated in a variety of animal models. The first patients with heart failure were treated with coenzyme Q10 by Yamamura et al. (1967). By mid 1980s it became apparent that it was safe and effective in the short-term treatment of patients with heart failure. Several long term trials were undertaken to evaluate its efficacy and safety using parameters like echocardiography. CoQ10 was added to standard treatments for heart failure such as diuretics, digitalis preparations (Lanoxin), and ACE inhibitors.

In 1994, a study conducted by Langsjoen et al. (1994a,b) illustrated the usefulness of CoQ10 in clinical cardiology. It tested CoQ10 in different types of myocardial diseases including ischemic cardiomyopathy, dilated cardiomyopathy, primary diastolic dysfunction, hypertensive heart disease and valvular heart disease etc Patients were treated with an average of 240 mg of CoQ10 per day and followed for up to 8 years. Significant improvement in NYHA functional classification was observed. 58% of patients improved by one NYHA class, 28% by two classes, and 1.2% by three NYHA classes. Myocardial function became measurably improved within 1 month with maximal improvement usually obtained by 6 months and this improvement was sustained in the majority of patients. The withdrawal of CoQ10 therapy resulted in a measurable decline in myocardial function within 1 month and a return to pretreatment measurements within three to 6 months. An average of 50% reduction in the requirement for concomitant cardiovascular drug therapy and a complete lack of toxicity were demonstrated.

Since this study, numerous other studies have demonstrated the benefit of CoQ10 supplementation in congestive heart failure related to primary cardiomyopathies or secondary forms of heart failure. It was concluded that supplemental treatment of CHF with CoQ10 is consistent with an improvement of stroke volume, ejection fraction, cardiac output, cardiac index and end diastolic volume index (Soja & Mortensen, 1997; Sander et al., 2006).Out of over a dozen studies conducted during the last two decades (Table 1) only a few trials failed to show any benefit (Watson et al. 1999; Khatta et al., 2000) corresponding to 10% of the total number of patients treated in double-blind trials. Dosage in these trials ranged from 60 to 200 mg/day with treatment periods ranging from 1 to 6 months. There was a 3.7% net improvement in ejection fraction (Sander et al., 2006). Treating 1000 patients for 1 year with study doses of CoQ10 prevented 200 hospitalisations due to worsening of CHF symptoms (Morisco et al., 1993).

7.4. Larger trials

Two large multicenter, open-label studies evaluated the efficacy and safety of CoQ10 as an adjuvant therapy in CHF. These two studies examined a total of more than 4000 patients with varying severity of CHF who experienced clinical improvement in signs and symptoms such as cyanosis, oedema, pulmonary rales, dyspnoea, and palpitations (Lampertico & Comis, 1993; Baggio et al., 1994).

Baggio et al. (1994) published the largest open trial in heart failure involving 2664 patients treated with up to 150 mg of CoQ10 per day, noting significant benefit and lack of toxicity. At the end of the three-month study period, the results indicated improvements in cyanosis (78.1%), edema (78.6%), pulmonary rales (77.8%), hepatomegaly (49.3%), jugular reflux (71.8%), dyspnea (52.7%), palpitations (75.4%), sweating (79.8%), vertigo (73.1%), subjective arrhythmia (63.4%), insomnia (62.8%) and nocturia (53.6%). Fifty-four percent of patients had improvements of at least three symptoms. Moreover, 28.8% of patients entered as NYHA class III improved in score to class II and 89.7% of patients entered as NYHA class II improved in score to class I. The authors concluded that patients receiving CoQ10 improved functionally and that patients in NYHA class II showed better improvement rates than did patients in NYHA class III.

7.5. Q-SYMBIO study (the planned SYMptoms, BIomarker status (BNP))

The encouraging results with CoQ10 in heart failure and need for further research constitute the background for the Q-SYMBIO study (Mortensen, 2003) is an ongoing multinational, double-blind, placebo-controlled trial. Approximately 550 patients in NYHA classes III–IV receiving standard therapy for chronic heart failure are being randomized to treatment with CoQ10 300 mg/day or placebo in parallel groups. It should help answer many of the unanswered questions.

7.6. Role in dilated cardiomyopathy (DCM)

Dilated cardiomyopathy is a form of cardiac muscle disease characterized by ventricular dilatation, contractile dysfunction and eventual congestive heart failure. 143 cases of DCM, 98% of whom were in NYHA classes II and IV, were given 100 mg of coenzyme Q10 orally in addition to their conventional medical programme in an open-label long term study. Mean ejection fraction of 44% rose to 60% within 6 months and stabilized at that level with 84% of patients showing statistically significant improvement. Eighty-five percent of patients improved by one or two NYHA classes. Survival figures were also encouraging (Langsjoen, 1990). Other trials confirmed these findings, showing that CoQ10 administration significantly improved the cardiac function in dilated cardiomyopathy and resistant heart failure (Mortensen et al., 1985).

7.7. Use in patients with end stage heart failure targetted for heart transplantation

In a randomized, double-blind, placebo-controlled trial, the effects of oral treatment with CoQ10 for 12 weeks was compared with placebo group (21 CoQ10 group A patients and 21 Placebo group B patients). Patients of heart failure were diagnosed by two dimensional/doppler echocardiography. After treatment for 12 weeks with CoQ10 there was significantly less dyspnoea, palpitation and weakness in the treated group as compared with the placebo. Diene conjugates, thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) which

Table 1
Latest study trials showing role of coenzyme Q_{10} in patients with chronic heart failure.

Author	Study design	No. of patients	NYHA class on entry	CoQ_{10} oral dosage (mg)	Treatment duration (months)	Results
Watson PS et al., 1999	Crossover	30	Unknown	33 t.i.d.	2×3	EF and SVR unaltered, left ventricular systolic and diastolic volume ↓
Khatta M et al., 2000	Two parallel groups	55	III–IV	200 q.d.	6	Exercise duration↑, EF unaltered, oxygen consumption ↑
Keogh MC Anne et al., 2003	Randomized double-blind, placebo-controlled	39	II–III Treated with ACEI	150 mg/day	3	NYHA class in the CoQ10 group: significant improvement of 0.5 class compared with the placebo ($n=18$) ($p=0.01$).,Specific Activities Scale class showed a significant ($p=0.004$) improvement in the CoQ10 group, but no change in the placebo group.,6-minute walk test distance ($p=0.047$) increase in the CoQ10 group with no change in the placebo group
Belardinelli R. et al., 2006	Double-blind, placebo-controlled crossover design	23	NYHA classes II and III with stable CHF secondary to ischemic heart disease [ejection fraction 37±7%]	100 mg t.i.d. with exercise training	2	As compared to exercise training (ET) plus placebo, CoQ10 plus ET showed significant improvement.CoQ10's main effect was: peak VO2 + 9%, endothelium-dependent dilation of the brachial artery (EDDBA) +38%, systolic wall thickening score index (SWTI) −12%; The combination of CoQ(10) and ET resulted in higher plasma CoQ(10) levels and more pronounced effects on all the abovementioned parameters. However, significant synergistic effect of CoQ(10) with ET was observed only for peak SWTI suggesting that ET amplifies the effect of CoQ(10) on contractility of dysfunctional myocardium.
Munkholm H. et al., 2008	Randomized double-blinded placebo-controlled	22	NYHA classes II–III with mean left ventricular (LV) ejection fraction 26%, mean LV internal diameter 71 mm	100 mg twice daily	3	A right heart catheterisation was done including a 3-minute exercise test. The stroke index at rest and work improved significantly, the pulmonary artery pressure at rest and work decreased (significantly at rest), and the pulmonary capillary wedge pressure at rest and work decreased (significantly at 1 min work).
Hosseini, 2008	Randomized placebo-controlled	50	NYHA classes II–III	100 mg daily	12	Significant increase in ejection fraction and improvement in symptoms

NYHA = New York Heart Association; EF = ejection fraction; SI = stroke index; CI = cardiac index; EDVI = end diastolic volume index; W = watts; SV = stroke volume; CO = cardiac output; EDV = end diastolic volume; SVR = systemic vascular resistance; PEP:LVET = preejection period:left ventricular ejection time ratio; QOL = quality of life.

are parameters of oxidative damage also significantly declined in CoQ10 group. There was also a significant reduction in left ventricular wall thickness, left ventricular mass, ejection fraction, endsystolic and end diastolic volumes in the CoQ10 treated group as compared to the placebo (Kumar et al., 2002). The administration of CoQ10 to heart transplant candidates led to a significant improvement in functional status, clinical symptoms, and quality of life. An important note to be made is that most patients of end stage heart failure are on warfarin oral anticoagulant therapy and concomitant CoQ10 therapy may decrease international normalised ratio (INR) in these cases.

7.8. Coenzyme Q10 in diastolic dysfunction

Diastolic dysfunction is one of the earliest identifiable signs of myocardial failure which accounts for 30–49% of heart failure cases. Patients with diastolic dysfunction have an impairment of the filling phase of the cardiac cycle which causes a major limitation in their ability to increase cardiac output. It causes either decreased left ventricular end diastolic volume or a compensatory increased left ventricular end diastolic pressure and leads to pulmonary venous hypertension and the syndrome of 'diastolic heart failure.' In the process of relaxation a great deal of ATP is required to re-establish trans-membrane Ca2+ gradients which allow the uncoupling of actin/myocin and relaxation. Alterations in energy metabolism may lead to diastolic dysfunction and subsequently maladaptive cardiac remodelling.

Left ventricular diastolic dysfunction is associated with increased mortality rates in patients of chronic heart failure independent of systolic function. In a study of effect of CoQ10 in diastolic dysfunction in hypertrophic cardiomyopathy (HCM) 200 mg/day of CoQ10 was added to the conventional treatment in 46 patients with HCM diagnosed clinically and by echocardiography (group I) (Kumar et al., 2007a,b). Cases of long standing hypertension were excluded. A comparable control group of 41 age/sex matched cases of HCM received only conventional therapy. The follow up period ranged from 9.4 months to 27.5 months (mean of 14.5 months). There was a significant improvement in the parameters like NYHA class ≥1, in quality of life (QOL), on 6-minute walk test, in diastolic dysfunction by ≥1 parameter and in mitral regurgitation ≥1 grade. Post treatment echocardiogram showed significant reduction in left ventricular outflow tract gradient ≥15 mm Hg in obstructive cases (12 out of 46) in the treatment group. The mean interventricular septal and posterior wall thickness showed a significant reduction. No patient in the treatment group had ventricular tachycardia whereas 4 cases in the control group had this arrhythmia. In both groups 1 patient was lost due to sudden cardiac death. (Fig. 1) Similar observations have been made by Langsjoen et al. (1997) and Langsjoen and Folkers (1993).Thus CoQ10 may be recommended as a safe, effective and promising adjuvant complementary therapy for diastolic heart failure in conditions like HCM.

7.9. HMG-CoA reductase inhibitors and Coenzyme Q10

Statins which are used to treat elevated blood cholesterol levels by blocking cholesterol biosynthesis also block CoQ10 biosynthesis (Folkers et al., 1990). The resulting lowering of blood CoQ10 level is due to the partially shared biosynthetic mevalonate pathway of CoQ10 and cholesterol. Statins can reduce serum levels of coenzyme Q10 by up to 40% along with reduction in cholesterol/LDL levels by inhibiting HMG-CoA reductase. This depletes the CoQ10 in patients with heart failure using statins and produces significant harmful effects which can be negated by oral CoQ10 supplementation (Ghirlanda et al., 1993).Recent studies have shown long term statin therapy to induce diastolic dysfunction in persons with initial normal cardiac function (Silver & Langsjoen., 2003).From 1990 to 2004, 13 controlled trials demonstrated significant CoQ10 depletion secondary

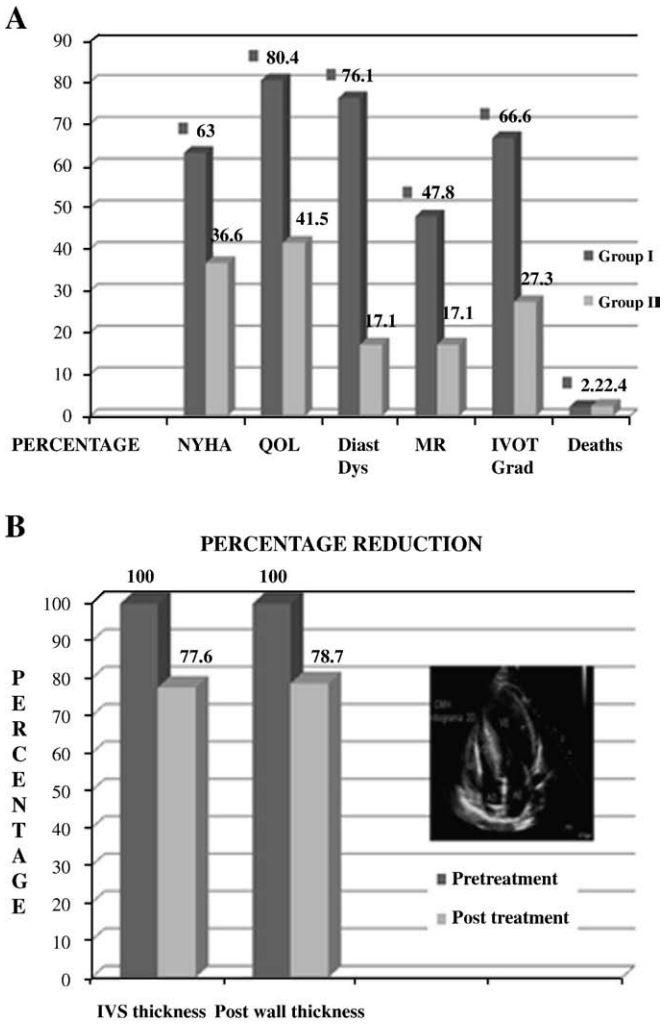

Fig. 1. Effect of coenzyme Q10 on patients of hypertrophic cardiomyopathy after a mean treatment period of 14.5 months. Group I (on adjunctive coenzyme Q10 therapy), Group II (not receiving CoQ10). Improvement in New York Heart Association (NYHA) class ≥1, improvement in quality of life (QOL) on detailed questionnaire, improvement in diastolic dysfunction by ≥1 parameter, improvement in mitral regurgitation (MR) ≥1 grade, significant reduction in left ventricular outflow tract (LVOT) gradient ≥15 mm Hg in obstructive cases, no. of deaths. (**A**): Significant reduction in interventricular thickness (IVS) and posterior wall thickness in post treatment period (9.4–27.5 months) (**B**).

to statin therapy (Hargreaves et al., 2005).Consequently, supplementing with CoQ10 is highly recommended to prevent the myopathic and other side effects associated with the statin drugs. In a study of 103 patients, statins along with CoQ10 produced beneficial effect in patients of ischemic dilated cardiomyopathy and the combination decreased the side effects of statins (Kumar et al., 2005a,b).

8. Role of Coenzyme Q10 in hypertension

8.1. Studies background

In animal models of hypertension, including spontaneously hypertensive rats, uninephrectomized rats treated with saline and deoxycorticosterone and experimentally hypertensive dogs, orally administered CoQ10 significantly lowered blood pressure. In another experimental study of hypertensive rats, a deficiency in the activity of succinate dehydrogenase CoQ10 reductase in leucocytes was found. (Iwamoto et al., 1974).Deficient activity of this enzyme can result in decreased levels of CoQ10. Having identified same deficiency in human subjects with chronic hypertension, investigators conducted a pilot study in which they concluded that increased succinate dehydrogenase CoQ10 reductase activity and subsequent increased CoQ10 level leads to decreases in systolic and diastolic blood pressures (Yamagami et al., 1974). Tissue deficiencies have been observed in patients of hypertension. Enzymatic deficiency of CoQ10 has been reported in 39% of hypertensive patients compared with only 6% of healthy controls.

8.2. Mechanism of action in hypertension

8.2.1. Effects on vascular endothelium

Although the mechanism behind CoQ10's antihypertensive effect is not conclusive, it is likely to be attributed to its ability to induce vasodilation via decreased peripheral resistance in the vasculature (Kamoto et al., 1991).

8.2.2. Antioxidant properties

Another hypothesis is that CoQ10's antioxidant properties result in quenching of free radicals that cause inactivation of endothelium-derived relaxing factor and/or fibrosis of arteriolar smooth muscle (Ignarro et al., 1989).

8.2.3. Improved diastolic function

With impairment of diastolic function, cardiac output can increase only by rise in catecholamines and increased heart rate. It is postulated that the blood pressure lowering effect of CoQ10 may in part be an indirect effect, whereby improved diastolic function leads to a lessening in the adaptive high catecholamine state of hypertensive disease (Langsjoen & Folkers, 1993).

8.2.4. Decrease in blood viscosity

It is also possible that the blood viscosity lowering effect of CoQ10 may favourably influence hypertension (Kato & Yoneda, 1990).

8.2.5. Effect on angiotensin and aldosterone

It is thought that coenzyme Q10 reduces aldosterone secretions and compromises the effect of angiotensin in sodium retention (Louis et al., 1965). There are several reports concerning the effect of CoQ10 on blood pressure in human studies. In an open-label study, doses of CoQ10 to maintain a serum level >2.0 μg/mL were added to standard antihypertensive drug therapy in 109 symptomatic patients with essential hypertension. The average daily dose of CoQ10 was 225 mg. Gradual improvements in functional and clinical status were observed within the first 6 months necessitating a decrease in antihypertensive drug therapy. Fifty-one percent of the patients were able to use 1–3 lesser antihypertensive drugs at an average of 4.4 months after starting CoQ10 treatment (Langsjoen et al., 1994a,b).

8.3. Meta-analysis of clinical antihypertensive trials

A recent meta-analysis of clinical trials investigating the use of CoQ10 for treatment of hypertension assessed its overall efficacy, consistency of therapeutic benefit and side effects (Rosenfeldt et al., 2007). It included twelve trials conducted since 1975 which examined a total of 362 hypertensive individuals, for a period of 8–12 weeks, and used daily CoQ10 doses of 100–120 mg. Four were prospective randomized trials and eight were before and after studies (in which the effect of CoQ10 on blood pressure was compared with the previous level). CoQ10 reduced systolic blood pressure by as much as 17 mmHg and diastolic blood pressure by up to 10 mmHg, without significant side effects. In many other trials, statistically significant decreases in systolic and diastolic blood pressure were observed with CoQ10 dosages that ranged from 30 to 360 mg/day in patients with hypertension. (Table 2). It has been shown to be particularly effective in hypertension in diabetics where it not only lowers blood pressure

Table 2
Studies showing effects of coenzyme Q_{10} in patients with hypertension.

Study design	Author	No. of patients	CoQ_{10} dosage (mg)	Treatment duration	Results
Placebo-controlled	Yamagami et al., 1986	20	33.3 t.i.d.	12 wks	SBP↓ (mm Hg): 167 vs. 148 ($p<0.001$ vs. baseline)
Cohort	Digiesi et al., 1994	26	50 b.i.d.	10 wks	SBP ↓ (mm Hg): 164.5 vs. 146.7 ($p<0.001$ vs. baseline) DBP↓ (mm Hg): 98.1 vs. 86.1 ($p<0.001$ vs. baseline) Serum TC↓ (mg/dl): 222.9 vs. 213 ($p<0.005$ vs. baseline)
Cohort	Langsjoen et al., 1994a,b	109	75–360 q.d. (mean 225 q.d.)	Mean 13 months	SBP ↓ (mm Hg): 159 vs. 147 ($p<0.001$ vs. baseline) DBP ↓ (mm Hg): 94 vs. 85 ($p<0.001$ vs. baseline) NYHA class improved: 2.40 vs. 1.36 ($p<0.001$ vs. baseline)
Placebo-controlled	Singh R et al., 1999	59	60 b.i.d.	8 wks	SBP ↓ (mm Hg): 164 vs. 152 ($p<0.05$ vs. placebo) DBP ↓ (mm Hg): 103 vs. 97 ($p<0.05$ vs. placebo)
Randomized, double-blind, placebo-controlled	Burke et al., 2001	46 men and 37 women with isolated systolic hypertension.	60 mg b.i.d	12 weeks	The mean reduction in systolic blood pressure of the CoQ10-treated group was 17.8 ± 7.3 mm Hg (mean ± SEM).
Randomized double-blind placebo-controlled	Hodgson et al., 2002	It was performed in 80 subjects with uncomplicated type 2 diabetes and dyslipidaemia	100 mg b.i.d	12 weeks	The main effect of CoQ 10 was to significantly decrease systolic (-6.1 ± 2.6 mmHg, $p = 0.021$) and diastolic (-2.9 ± 1.4 mmHg, $p = 0.048$) blood pressure and HbA1c ($-0.37 \pm 0.17\%$, $p = 0.032$).

but also improves diabetic control perhaps by improving insulin resistance. It is important to note that in all these clinical trials, CoQ10 was used in addition to traditional antihypertensive medical treatments and not alone.

Kimura and Kimura (2008) have recently reported a case of 67 year old woman with essential hypertension with a maximum blood pressure of 155/100 mm Hg who had been prescribed candesartan cilextil as an outpatient for about 5 years and did not respond to it and she frequently experienced side effects. After administration of CoQ10 her diastolic blood pressure normalised within 1 week and the systolic blood pressure after 1 month and she was later able to discontinue the antihypertensive drug.

It is interesting to note that beta-blocker medication inhibits CoQ10 dependent enzymes and possibly compromise their effect by causing CoQ10 deficiency on long term use. It should be noted that the effect of CoQ10 on blood pressure was usually not seen until after 4–12 weeks of therapy. This observation is consistent with the delayed increase in enzyme activity that results from administration of CoQ10. Thus, CoQ10 is not a typical antihypertensive drug; rather, it seems to correct some metabolic abnormality that is involved in the pathogenesis of hypertension.

9. Role in ischemic heart disease (IHD)

Controlled trials in IHD did not begin until the mid 1980s with the first publication by Hiasa et al. (1984) in which 18 patients were randomized to receive either intravenous CoQ10 or placebo. The treated patients showed an increase in exercise tolerance of one stage or greater in modified Bruce protocol as compared to the placebo group, with less ST-segment depression on exercise and experienced less angina with no alteration in heart rate or blood pressure. A year later, Kamikawa et al. (1985) studied 12 patients with chronic stable angina in a double-blind placebo-controlled randomized crossover protocol using 150 mg a day of oral CoQ10. Exercise time increased significantly from 345 s to 406 s with CoQ10 treatment and time until 1 mm of ST depression increased significantly from 196 s to 284 s ($p<0.01$). Schardt et al. (1986) studied 15 patients with exercise-induced angina treated with 600 mg/day of CoQ10 with a placebo-controlled double-blind crossover design and noted similar results. Since the CoQ10 treatment caused no significant alteration in heart rate or blood pressure, it was concluded that the mechanism of action was related to a direct effect on myocardial metabolism. A trial conducted by Wilson et al. (1991) showed similar benefit including a significant reduction in the number of anginal episodes and nitrate consumption. In a recent study (Kumar et al., 2005a,b) on 106 cases of acute coronary syndrome which included non-ST elevation myocardial infarction and unstable angina, adjunctive CoQ10 therapy produced symptomatic improvement in anginal scores and resulted in decreased development of significant left ventricular dysfunction by clinical/echocardiographic criteria and a decreased need for revascularisation therapy by percutaneous transluminal coronary angioplasty/coronary artery bypass surgery with a lesser mortality at 6 months follow up (Fig. 2).

The role of free radicals in cell injury and cell death in settings of ischemia and reperfusion is becoming increasingly well established. CoQ10's antioxidant properties and its location within the mitochondria (the centre of free radical production) make it an obvious candidate for a potential therapeutic agent in this situation (Yokoyama et al., 1996).It also improves myocardial ischemia by improving coronary vasodilatation and by improving endothelial function. Reactive oxygen species seem to play an important role in vascular homeostasis. In conditions of high oxidative stress such as coronary artery disease, the rate of inactivation of nitric oxide to peroxynitrite by superoxide anions may be reduced by CoQ10. Patients with lower levels of extracellular superoxide dismutase (ecSOD) demonstrate greater improvements than patients with normal ecSOD levels, suggesting that higher the oxidative stress

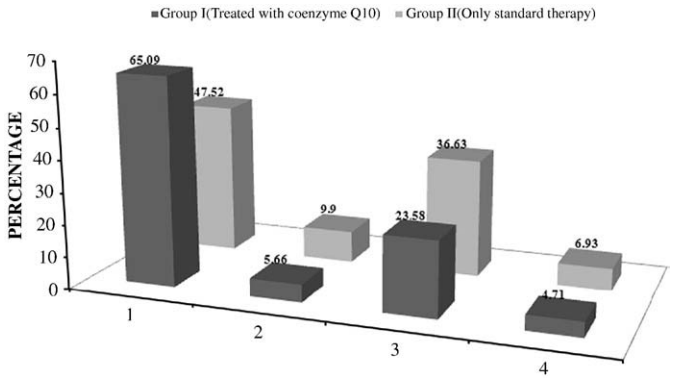

Fig. 2. Comparison of end point parameters after adjunctive coenzyme Q10 therapy in 106 cases of acute coronary syndrome. Parameters: 1-symptomatic improvement on anginal scoring system, 2-development of significant left ventricular dysfunction, 3-need for revascularisation by percutaneous transluminal angioplasty or coronary artery bypass, and 4-end point mortality.

greater is the improvement in the endothelium-dependent relaxation after the administration of CoQ10 (Belardinelli et al., 2008).

It may also influence vascular function indirectly via inhibition of oxidative damage to LDL (Stoker et al., 1991) and prevention of atherosclerosis.CoQ10 is crucial for preservation of oxidative phosphorylation and reduction of myocardial damage during conditions of metabolic stress. The mechanism for improved exercise tolerance in patients with stable angina may be due to ischemic myocardial protection by CoQ10, allowing tissue to reach higher levels of energy expenditure (Crane, 2001).

CoQ10 also decreases blood viscosity and improves blood flow to cardiac muscle in patients with ischemic heart disease (Kato & Yoneda, 1990). It also helps in ischemic heart disease by decreasing the inflammatory cytokines and prevents the hypergycemia induced endothelial cell damage, monocyte adhesion and evolution of atherosclerotic lesions in diabetic patients (Tsuneki et al., 2007).

In acute myocardial infarction, in recent trials, use of CoQ10 produced significant reduction in postinfarct angina, left ventricular dysfunction and arrhythmias due to prevention of QT prolongation by optimising membrane repolarization although there was no significant change in the mortality pattern. A study of 144 patients with acute myocardial infarction (AMI) that was published in 1998 demonstrated a halving of total cardiac events in those given CoQ10 compared with placebo. In another randomized double-blind controlled trial involving 71 patients, oral treatment with coenzyme Q10 (120 mg/day) after 1 year showed that total cardiac events were 24.6% vs. 45.0% ($p<0.02$) including non-fatal infarction 13.7% vs. 25.3% ($p<0.05$) and cardiac deaths were significantly lower in the intervention group compared to control group. The extent of cardiac disease, elevation in cardiac enzymes, left ventricular enlargement and previous coronary artery disease showed no significant differences between the two groups (Singh et al., 1998, 2003).

10. Role in arrhythmias

There is some anecdotal experimental and clinical evidence of a beneficial effect of coenzyme Q10 in cardiac arrhythmias. This effect could be due to improvement of cellular membrane function and energy production and reduction of the myocardial ischemia that can generate arrhythmias. In heart failure there is Ca2+ overload due to decreased uptake by the sarcoplasmic reticulum associated with depressed diastolic energetics. This results in increased Na+/Ca2+ exchange activity. Calcium efflux is associated with Na+ influx which can prolong depolarization and cause after depolarizations. (Schillingera et al., 2003). CoQ10 has a beneficial effect on arrhythmias possibly due to improved energetics in the above situation.

Twenty-seven patients with ventricular premature beats (VPBs) and no evidence of organic heart disease received a placebo for 3–4 weeks, followed by 60 mg/day of coenzyme Q10 for 4–5 weeks. The reduction in VPBs was significantly greater after CoQ10 than after placebo. The beneficial effect of CoQ10 was seen primarily in diabetics, in whom the mean reduction in VPB frequency was 85.7%. A significan reduction in VPBs also occurred in 1 (11%) of 9 otherwise healthy patients and in 4 (36%) of 11 patients with hypertension (Fujioka et al., 1983). Kuklinski et al. (1994) studied 61 patients with acute myocardial infarction, randomized to obtain either placebo or 100 mg of CoQ10 with 100 mg of selenium for a period of 1 year. The treatment group showed no prolongation of the corrected QT-interval whereas, in the placebo group, 40% showed prolongation of the corrected QT-interval of greater than 440 ms ($p<0.001$). Although there were no significant differences in the acute hospitalisation, the 1 year follow up revealed six patients (20%) in the control group died from re-infarction, whereas one patient in the treatment group suffered a noncardiac death. The prevention of QT-interval prolongation can be explained by an enhancement in myocardial bioenergetics with an improvement in sodium–potassium ATPase function, thereby optimising membrane repolarization and decreasing occurrence of dangerous arrhythmias like ventricular tachycardia and ventricular fibrillation (Greenberg & Frishman, 1990).

11. Protection during cardiac surgery

Postoperative low cardiac output is a major cause of early death following cardiac surgery. Coenzyme Q10 has been used in the cardiothoracic surgical setting in order to offset reperfusion-related increases in free radical formation and oxidative stress. From 1982 to 2004 at least eight controlled trials of CoQ10 in cardiac surgery have been published. All but one of these trials has shown a beneficial effects of some kind. The one trial showing an absence of effect (Taggart et al., 1996) used oral CoQ10 for only 12 h before surgery, an inadequate time frame for sufficient dosing to increase myocardial levels.

Chello et al. (1994) randomized 40 patients to receive either placebo or 150 mg/day of oral CoQ10 1 week prior to coronary artery bypass graft surgery. A significant decrease in postoperative markers of oxidative damage was observed in the treatment group with lower concentrations of coronary sinus thiobarbituric acid reactive substances, conjugated dienes and cardiac isoenzymes of creatine kinase. The treatment group also showed a significantly lower incidence of ventricular arrhythmias in the recovery period and the mean dose of dopamine required to maintain stable hemodynamics was significantly lower in the CoQ10 treated group. Prior treatment with CoQ10 2 weeks before coronary artery bypass surgery or valve replacement lead to decreased requirement of ionotropic drugs, improved left ventricular function indices and shorter recovery time. Another prospective randomized placebo-controlled trial of 300 mg/day of oral CoQ10 for 2 weeks preoperatively in 121 coronary bypass or valve replacement procedures by Rosenfeldt et al. (2005) showed increased mitochondrial CoQ10 content, increased efficiency of mitochondrial energy production and improved contractile function in myocardial trabeculae and better postoperative surgical results.

12. Role in doxorubicin cardiotoxicity

Recent trials with anticancer drug Doxorubicin (Adriamycin) including those in animal models, have noted a reduction in cardiac coenzyme Q10 depletion and cardiotoxicity associated with coadministration of coenzyme Q10 (Judy et al., 1984). Addition of 50 mg/day of CoQ10 along with adriamycin significantly reduced cardiotoxicity on long term use.

13. Role in mitral valve prolapse (MVP) syndrome

There are reports of some benefit of CoQ10 in mitral valve prolapse (MVP) syndrome with symptomatic improvement and better handgrip strength in some cases. In a study of 27 cases of MVP syndrome by Langsjoen and Langsjoen (1999) use of CoQ10 resulted in symptomatic improvement with better diastolic function in majority of the cases.

14. Role in Meniere-like syndrome

As far back as 1988, researchers were aware that CoQ10 was effective in promoting recovery from acute sudden deafness. A Japanese study was conducted on guinea pigs with acute sensorineural hearing loss artificially induced by hypoxia (lack of oxygen) conditions. The results showed that CoQ10 “is effective in promoting recovery from damage to auditory hairs as well as in preventing respiratory metabolic impairment of hair cells due to hypoxia” (Yao et al., 2004).

Oxidative stress causes ischemia due to oxidation of proteins and lipids and could be among the etiological factors in the genesis of

hearing disorders. In patients with a low plasma CoQ10 concentration, CoQ10 supplementation may decrease the tinnitus expression. In a preliminary trial, the effects of CoQ10 were studied on patients with tinnitus. The study involved 20 patients with tinnitus and lasted for 16 weeks. CoQ10 levels were recorded before the study began. Tinnitus questionnaire (TQ) was used to evaluate efficacy. Patients were given CoQ10 100 mg three times daily. At the end of the study the mean plasma concentration of CoQ10 significantly increased and was still elevated 4 weeks after the study ended. No statistical differences in tinnitus questionnaire scores were recorded. However, a subgroup of 7 patients had significant reductions in questionnaire scores from 38 to 24. These responders had a reduction in all dimensions of the TQ score compared with their initial values except for the dimension of emotional distress. The patients in this group who responded well had a much lower level of CoQ10 before the study began than non-responders. Moreover, the increase of CoQ10 levels was significantly higher in responders than in non-responders. Supplementation with coenzyme Q10 for 16 weeks significantly improved tinnitus in people who had initially low blood levels of CoQ10 (Khan et al., 2007).

During a large multicenter clinical trial of 2664 patients with congestive heart failure, 73.1% cases who had experienced vertigo reported a decrease in the symptom after 3 months of treatment with 50 to 150 mg of CoQ10 daily (Baggio et al., 1994). In another recent case report by Kimura and Kimura (2008), a hypertensive patient on CoQ10 also experienced considerable relief from his Meniere disease like symptoms.

15. Conclusion

Coenzyme Q10 is a critical adjuvant therapy for patients with cardiac diseases due to its beneficial effects on cellular bioenergetics, regulation of cell membrane channels and its antioxidant effect. It may allow for a reduction of other pharmacological therapies, improvement in quality of life and a decrease in the incidence of complications. However, dosing, clinical application, bioavailability and dissolution of CoQ10 deserve careful scrutiny whenever employing this nutrient. The assessment of blood levels in 'therapeutic failures' appears warranted. It produces maximum improvement in heart failure cases with diastolic and systolic dysfunction where its beneficial role is well established especially on the 'quality of life' and reduction in number of hospitalisations although mortality benefits are not clearly seen. Favourable effects have been observed in patients of hypertension allowing decrease in other antihypertensive medication. The available trials also show improvement in exercise tolerance and generally beneficial effects in cases of ischemic heart disease, arrhythmias and cardiac surgery and also in Meniere-like hearing disturbances. The smaller number of patients and shorter duration of most of the trials underline the need for further research in this regard. Coenzyme Q10 may be ushering in a new era of cellular/biochemical treatment, complementing the existing approach of treating cardiovascular diseases.

References

Baggio, E., Gandini, R., Plancher, A. C., Passeri, M., & Carmosino, G. (1994). Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure. *Mol Aspects Med 15*(suppl), S287–S294.

Belardinelli, R., Muçaj, A., Lacalaprice, F., Solenghi, M., Seddaiu, G., Principi, F., et al. (2006). Coenzyme Q10 and exercise training in chronic heart failure. *Eur Heart J 27*(22), 2675–2681.

Belardinelli, R., Tiano, L., & Littarru, G. P. (2008). Oxidative stress, endothelial function and coenzyme Q10. *BioFactors 32*(1–4), 129–133.

Burke, B. E., Neuenschwander, R., & Olson, R. D. (2001). Randomized, double-blind, placebo-controlled trial of coenzyme q10 in isolated systolic hypertension. *South Med J 94*(11), 1112–1117.

Chello, M., Mastroroberto, P., Romano, R., Bevacqua, E., Pantaleo, D., Ascione, R., et al. (1994). Protection by coenzyme Q10 from myocardial reperfusion injury during coronary artery bypass grafting. *Ann Thorac Surg 58*, 1427–1432.

Crane, F. L. (2001). Biochemical functions of coenzyme Q10. *J Am Coll Nutr 20*(6), 591–598.

Crane, F. L., Hatefi, Y., Lester, R. I., & Widmer, C. (1957). Isolation of a quinone from beef heart mitochondria. *Biochim Biophys Acta 25*, 220–221.

Crestanello, J. A., Kamelgard, J., Lingle, D. M., Mortensen, S. A., Rhode, M., & Whitman, G. J. (1996). Elucidation of a tripartite mechanism underlying the improvement in cardiac tolerance to ischemia by coenzyme Q10 pretreatment. *J Thorac Cardiovasc Surg 111*(2), 443–450.

Digiesi, V., Cantini, F., Oradei, A., Bisi, G., Guarino, G. C., Brocchi, A., et al. (1994). Coenzyme Q10 in essential hypertension.*Mol Aspects Med 15*, 257–263 (suppl).

Ellin, J. M., Batz, F., & Hitchens, K. (1999). *Coenzyme Q10. Pharmacist's letter/prescriber's letter: Natural medicines comprehensive database* (pp. 172–173). Stockton, CA: Therapeutic Research Center.

Folkers, K., Littarru, G. P., Ho, L., Runge, T. M., Havanonda, S., & Cooley, D. (1970). Evidence for a deficiency of coenzyme Q10 in human heart disease. *Int J Vitam Nutr Res 40*, 380–390.

Folkers, K., Vadhanavikit, S., & Mortensen, S. A. (1985). Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. *Proc Natl Acad Sci 82*, 901–904.

Folkers, K., Langsjoen, H., Willis, R., Richardson, P., Xia, L., Ye, C., et al. (1990). Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci 87*, 8931–8934.

Fujioka, T., Sakamoto, Y., & Mimura, G. (1983). Clinical study of cardiac arrhythmias using a 24-hour continuous electrocardiographic recorder (5th report) — antiarrhythmic action of coenzyme Q10 in diabetics. *Tohoku J Exp Med 141*(Suppl), 453–463.

Ghirlanda, G., Oradei, A., Manto, A., Lippa, S., Uccioli, L., Caputo, S., et al. (1993). Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double blind, placebo-controlled study. *Clin Pharmocol J 33*(3), 226–229.

Greenberg, S., & Frishman, W. H. (1990). Co-enzyme Ql0: a new drug for cardiovascular disease. *J Pharmacol 30*, 596–608.

Hargreaves, I. P., Duncan, A. J., Heales, S. J., & Land, J. M. (2005). The effect of HMG-CoA reductase inhibitors on coenzyme Q10: possible biochemical/clinical implications. *Drug Saf 28*, 659–676.

Hathcock, J. N., & Shao, A. (2006). Risk assessment for coenzyme Q10 (ubiquinone). *Regul Toxicol Pharmacol 45*, 282–288.

Hiasa, Y., Ishida, T., Maeda, T., Iwanc, K., Aihara, T., & Mori, H. (1984). In K. Folkers & Y. Yamamura (Eds.), Effects of coenzyme Q10 in patients with stable angina pectoris. *Biomedical and Clinical Aspects of Coenzyme Q Vol. 4*. (pp. 291–301) Amsterdam: Elsevier Science.

Hodgson, J. M., Watts, G. F., Playford, D. A., Burke, V., & Croft, K. D. (2002). Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. *Eur J Clin Nutr 56*(11), 1137–1142.

Hosoe, K., Kitano, M., Kishida, H., Kubo, H., Fujii, K., & Kitahara, M. (2007). Study on safety and bioavailability of ubiquinol after single and 4-week multiple oral administration to healthy volunteers. *Regul Toxicol Pharmacol 7*(1), 19–28.

Hosseini, V. N. (2008). Comparison of coenzyme Q10 versus placebo in chronic heart failure. *Res J Biol Sci 3*(6), 546–549.

Ignarro, L. J. (1989). Biological actions and properties of endothelium-derived nitric oxide formed and released from artery and vein. *Circ Res 65*, 1–21.

Iwamoto, Y., Yamaguchi, T., & Folkers, K. (1974). Deficiency of coenzyme Q10 in hypertensive rats and reduction of deficiency by treatment with coenzyme Q10. *Biochem Biophys Res Commun 58*, 743–748.

Judy, W.V., Hall, J.H., Dugan, W. (1984). Coenzyme Q10 reduction of adriamycin cardiotoxicity. In Biomedical and Clinical Aspects of Coenzyme Q, Vol. 4, ed. K Folkers, Y Yamamura. Amsterdam: Elsevier/North Holland Biomedical Press, 231–241.

Kamikawa, T., Kobayashi, A., Yamashita, T., Hayashi, H., & Yamazaki, N. (1985). Effects of coenzyme Q10 on exercise tolerance in chronic stable angina pectoris. *Am J Cardiol 56*, 247–251.

Kamoto, H., Kawaguchi, H., & Togashi, H. (1991). Effect of coenzyme Q10 on structural alterations in the renal membrane of stroke-prone spontaneously hypertensive rats. *Biochem Med Metab Biol 45*, 216–226.

Kato, T., & Yoneda, S. (1990). Reduction in blood viscosity by treatment with coenzyme Q10 in patients with ischemic heart disease. *Int J Clin Pharmacol Ther Toxicol 28*(3), 123–126.

Kayo, C. Y., & Carsten, M. E. (2005). *Cellular Aspects of Smooth Muscle Function.*: Cambridge University Press Chapter 6 p 209.

Keogh, A., Fenton, S., Leslie, B., Christina, A. B. S., Macdonald, P., Zhao, Y. C., et al. (2003). Randomised double-blind, placebo-controlled trial of coenzyme Q10 therapy in class II and III systolic heart failure. *Heart Lung Circ 12*(3), 135–141.

Khan, M., Gross, J., & Haupt, H. (2007). A pilot clinical trial of the effects of coenzyme Q10 on chronic tinnitus aurium. *Otolaryngol Head Neck Surg 136*, 72–77.

Khatta, M., Alexander, B. S., Krichten, C. M., Fisher, M. L., Freudenberger, R., Robinson, S. W., et al. (2000). The effect of coenzyme Q10 in patients with congestive heart failure. *Ann Intern Med 132*, 636–640.

Kimura, I., & Kimura, M. (2008). Can coenzyme Q10 lead to improvement of essential hypertension? A long-term case study. *J Health Sci 54*(5), 571–575.

Kuklinski, B., Weissenbacher, E., & Fahnrich, A. (1994). Coenzyme Q10 and antioxidants in acute myocardial infarction.*Mol Aspects Med 15*(Suppl), 143–147 s.

Kumar, A., Kartikey, N. S., Niaz, M. A., & Singh, R. B. (2002). Effect of Q gel (coenzyme Q10) in patients with end stage heart failure targetted for heart transplantation. *Third Conference of the International Coenzyme Q10 Association, London, UK*.

Kumar, A., Kaur, H., & Mohan, V. (2005). *Adjunctive Coenzyme Q10 Therapy in 106 Cases of Acute Coronary Syndrome (ACS) Fourth Conference of the International Coenzyme Q10 Association, LA, USA*.

Kumar, A., Kaur, H., & Mohan, V. (2005). Atorvastatin alone/in combination with co-enzyme Q10 in 103 cases of ischemic dilated cardiomyopathy. *Fourth Conference of the International Coenzyme Q10 Association, LA, USA*.

Kumar, A., Kaur, H., & Mohan, V. (2007). Coenzyme Q10 in isolated diastolic heart failure in hypertrophic cardiomyopathy (HCM). *The 5th Conference of the International Coenzyme Q10 Association, Kobe Japan*.

Kumar, A., Singh, R. B., Saxena, M., Mohammad, N. A., Joshi, S. R., Chattopadhyay, P., et al. (2007). Effect of CarniQgel (ubiquinol and carnitine) on cytokines in patients with heart failure in the Tishcon study. *Acta Cardiol 62*(4), 349–354.

Lampertico, M., & Comis, S. (1993). Italian multicenter study on the efficacy and safety of coenzyme Q10 as adjuvant therapy in heart failure. *Clin Invest 71*(8), 129–133.

Langsjoen, P. H. (1990). A six-year clinical study of therapy of cardiomyopathy with coenzyme Q10. *Int J Tissue React 12*(3), 169–171.

Langsjoen, P. (2007, November 9–12). *5th Annual International CoQ10 Symposium. Kobe, Japan*.

Langsjoen, P. H., & Folkers, K. (1993). Isolated diastolic dysfunction of the myocardium and its response to CoQ10 treatment. *Clin Investig 71*(8 Suppl), S140–S144.

Langsjoen, P. H., & Langsjoen, A. M. (1999). Overview of the use of CoQ10 in cardiovascular disease. *Biofactors 9*(2–4), 273–284.

Langsjoen, H., Langsjoen, P., Langsjoen, P., Willis, R., & Folkers, K. (1994). Usefulness of coenzyme Q10 in clinical cardiology: a long-term study.*Mol Aspects Med 15*, s165–s175 Suppl.

Langsjoen, P., Willisb, R., & Folkers, K. (1994). Treatment of essential hypertension with coenzyme Q10. *Mol Aspects Med 15*, 262–272.

Langsjoen, P. H., Langsjoen, A., Willis, R., & Folkers, K. (1997). Treatment of hypertrophic cardiomyopathy with coenzyme Q10. *Mol Aspects Med 18*(Suppl), S145–S151.

Littarru, G. P., & Tiano, L. (2007). Bioenergetic and antioxidant properties of coenzyme q10: recent developments. *Mol Biotechnol 37*, 31–37.

Littarru, G. P., Ho, L., & Folkers, K. (1972). Deficiency of coenzyme Q10 in human heart disease. Part I. *Int J Vitam Nutr Res 42*, 291–305.

Louis, F., Fabre, J. R., Robert, C., Banks, I., William, M., McIsaac, I., et al. (1965). Effects of ubiquinone and related substances on secretion of aldosterone and cortisol. *Am J Physiol 208*, 1275–1280.

Marin-Garcia, J., Goldenthala, M. J., & Moe, G. W. (2001). Mitochondrial pathology in cardiac failure. *Cardiovasc Res 49*(1), 17–26.

Marin-Garcia, J., Goldenthal, M. J., Pierpont, M. E., & Ananthakrishnan, R. (1995). Impaired mitochondrial function in idiopathic dilated cardiomyopathy: biochemical and molecular analysis. *J Card Fail 1*, 285–292.

Masaru, K., Yu, Y., Satomi, K., & Kazumasa, O. M. (2008). Beneficial effect of coenzyme Q10 on increased oxidative and nitrative stress and inflammation and individual metabolic components developing in a rat model of metabolic syndrome. *J Pharmacol Sci 107*(2), 128–137.

Mellors, A., & Tappel, A. L. (1966). Quinone and quinols as inhibitors of lipid peroxidation. *Lipids 1*, 282–284.

Molyneux, S. L., Young, J. M., Florkowski, C. M., Lever, M., & George, P. M. (2008). Coenzyme Q10: is there a clinical role and a case for measurement? *Clin Biochem Rev 29*, 71–82.

Molyneux, S. L., Florkowski, C. M., George, P. M., Pilbrow, A. P., Frampton, C. M., Lever, M., et al. (2008). Coenzyme Q10: an independent predictor of mortality in chronic heart failure. *Am Coll Cardiol 52*, 1435–1441.

Morisco, C., Trimarco, B., & Condorelli, M. (1993). Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study. *J Mol Med Issue 71*(Supplement 8), S134–S136.

Mortensen, S. A. (2003). Overview on coenzyme Q10 as adjunctive therapy in chronic heart failure. Rationale, design and end-points of "Q-symbio"—a multinational trial. *Biofactors 18*, 79–89.

Mortensen, S. A., Vadhanavikit, S., & Folkers, K. (1984). Deficiency of coenzyme Q10 in myocardial failure. *Drugs Exp Clin Res 10*(7), 497–502.

Mortensen, S. A., Vadhanavikit, S., Baandrup, U., & Folkers, K. (1985). Long-term coenzyme Q10 therapy: a major advance in the management of resistant myocardial failure. *Drugs Exp Clin Res 11*(8), 581–593.

Munkholm, H., Hansen, H. H., & Rasmussen, K. (2008). Coenzyme Q10 treatment in serious heart failure. *BioFactors 9*(2–4), 285–289.

Nakamura, T., Sanma, H., Himeno, M., and Kato, K. (1980).Transfer of exogenous coenzyme Q10 to the inner membrane of heart mitochondria in rats. K. Folkers, Y. Yamamura (Eds.) Biomedical and clinical aspects of coenzyme Q. Elsevier/North-Holland Press, 2:3–14.

Redalieu, E., Nilsson, I. M., Farley, T. M., Folkers, K., & Koniuszy, F. R. (1968). Determination and levels of coenzyme Q10 in human blood. *Anal Biochem 23*(1), 132–140.

Rosenfeldt, F., Marasco, S., Lyon, W., Wowk, M., Sheeran, F., Bailey, M., Esmore, D., Davis, B., Pick, A., et al. (2005). Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and in vitro contractility of myocardial tissue. *J Thorac Cardiovasc Surg 129*, 25–32.

Rosenfeldt, F. L., Haas, S. J., Krum, H., Hadj, A., Ng, K., Leong, J. Y., et al. (2007). Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. *J Human Hypertens 21*, 297–306.

Rustin, P., Lebidois, J., & Chretien, D. (1994). Endomyocardial biopsies for early detection of mitochondrial disorders in hypertrophic cardiomyopathies. *J Pediatr 124*, 224–228.

Sander, S., Coleman, C. I., Patel, A. A., Kluger, J., & White, C. M. (2006). The impact of coenzyme Q10 on systolic function in patients with chronic heart failure. *J Card Fail 12*, 464–472.

Schardt, F., Welzel, D., Schiess, W., & Toda, K. (1986). In K. Folkers & Y. Yamamura (Eds.), *Effect of coenzyme Q10 on ischemia-induced ST-segment depression: a double-blind, placebo-controlled crossover studyBiomedical and Clinical Aspects of Coenzyme Q Vol. 5*. (pp. 358–394) Amsterdam: Elsevier Science Publishers BV.

Schillingera, W., Fioletb, J. W., Schlotthauera, K., & Hasenfuss, G. (2003). Relevance of Na^{+}–Ca^{2+} exchange in heart failure. *Cardiovasc Res 57*(4), 921–933.

Silver, M. A., & Langsjoen, P. H. (2003). Statin cardiomyopathy: a potential role for coenzyme Q10 therapy for statin induced changes in diastolic LV performance: description of a clinical protocol. *Bio factors 18*(1–4), 125–127.

Singh, R. B., Wander, G. S., Rastogi, A., Shukla, P. K., Mittal, A., Sharma, J. P., et al. (1998). Randomized, double-blind placebo controlled trial of coenzyme Q10 in patients with acute myocardial infarction. *Cardiovasc Drugs Ther 12*, 347–353.

Singh, R. B., Niaz, M. A., & Rastogi, S. S. (1999). Effect of hydrosoluble coenzyme Q10 on blood pressure and insulin resistance in hypertensive patients with coronary artery disease. *J Hum Hypertens 13*, 203–208.

Singh, R. B., Neki, N. S., Kartikey, K., Pella, D., Kumar, A., Niaz, M. A., et al. (2003). Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction. *Mol Cell Biochem 246*(1–2), 75–82.

Soja, A. M., & Mortensen, S. A. (1997). Treatment of congestive heart failure with coenzyme Q10 illuminated by meta-analyses of clinical trials. *Mol Aspects Med 18*, 159–168.

Stoker, R., Bowry, V. W., & Frei, B. (1991). Ubiquinol-10 protects human low density lipoprotein more efficiently against lipid peroxidation than does a-tocopherol. *Proc Natl Acad Sci 88*, 1646–1650.

Taggart, D. P., Jenkins, M., Hooper, J., Hadjinikolas, L., Kemp, M., Hue, D., et al. (1996). Effects of short-term supplementation with coenzyme Q10 on myocardial protection during cardiac operations. *Ann Thorac Surg 61*(3), 829–833.

Tiano, R., Belardinelli, P., Carnevali, F., Principi, G., Seddaiu, & Littarru, G. P. (2007). Effect of coenzyme Q10 administration on endothelial function and extracellular superoxide dismutase in patients with ischaemic heart disease: a double-blind, randomized controlled study. *Eur Heart J 28*(18), 2249–2255.

Tsuneki, H., Sekizaki, N., Suzuki, T., Kobayashi, S., Wada, T., Okamoto, T., et al. (2007). Coenzyme Q10 prevents high glucose-induced oxidative stress in human umbilical vein endothelial cells. *Eur J Pharmacol 566*(1–3), 1–10.

Vogt, A. M. (1998). Heart failure: is there an energy deficit contributing to contractile dysfunction? *Basic Res Cardiol 93*(1), 1–10.

Watson, P. S., Scalia, G. M., Galbraith, A., Burstow, D. J., Bett, N., & Aroney, C. N. (1999). Lack of effect of coenzyme Q on left ventricular function in patients with congestive heart failure. *J Am Coll Cardiol 33*, 1549–1552.

Wilson, M. F., Frishman, W. H., Giles, T., Sethi, G., Greenberg, S. M., & Brackett, D. J. (1991). Coenzyme Q10 therapy and exercise duration in stable angina. In K. Folkers, G. P. Littarru, & T. Yamagami (Eds.), *Biomedical and Clinical Aspects of Coenzyme Q Vol. 6*. (pp. 339–348)Amsterdam: Elsevier.

Yamagami, T., Iwamoto, Y., & Folkers, K. (1974). Deficiency of activity of succinate dehydrogenase-coenzyme Q10 reductase in leukocytes from patients with essential hypertension. *Int J Vitam Nutr Res 44*, 404–414.

Yamagami, T., Takagi, M., & Akagami, H. (1986). In K. Folkers, & Y. Yamamura (Eds.), *Effect of coenzyme Q10 on essential hypertension: a double-blind controlled study- Vol. 5*. (pp. 337–343) Amsterdam: Elsevier Science Publishers BV.

Yamamura, Y., Ishiyama, T., Yamagami, T., Morita, Y., Ishio, S., Kashiwamura, S., et al. (1967). Clinical use of coenzyme-Q for treatment of cardiovascular disease. *Jpn Circ J 31*, 168.

Yao, Z. X., Han, Z., Drieu, K., & Papadopoulos, V. (2004). Ginkgo biloba extract (EGb 761) inhibits beta-amyloid production by lowering free cholesterol levels. *Nutr Biochem 15*(12), 749–756.

Yokoyama, H., Lingle, D. M., Crestanello, J. A., Kamelgard, J., Kott, B. R., Momeni, R., et al. (1996, Aug). Coenzyme Q10 protects coronary endothelial function from ischemia reperfusion injury via an antioxidant effect. *Surgery 120*(2), 189–196.