Coenzyme Q10 And The Heart*

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Summary:

Coenzyme Q10 (ubiquinone) is normally present in every plant and animal cell. It is synthesised in all body tissues and to resolve the controversy in nomenclature, it should be called antioxidant because of its free radical scavenging action. Coenzyme Q10 deficiency can occur due to insufficient intake, impairment in biosynthesis or excessive utilization by the body tissues or any combination of the three. While dietary deficiency may be a risk factor of diseases due to free radical stress, there is a greater endogenous consumption of coenzyme Q10 in certain diseases associated with ischaemia and reperfusion and oxidative stress. Coenzyme Q10 deficiency has been observed among patients with conjestive heart failure, angina pectoris, coronary artery disease cardiomyopathy, hypertension, mitral valve prolapse and after coronary revascularization. Coenzyme Q10 is involved in the manufactue of ATP which is potentially useful in preventing cellular damage during ischaemia - reperfusion. The clinical benefits are mainly due to its ability to improve energy production, antioxidant activity, and membrane stabilizing properties. Several uncontrolled studies and about ten randomized controlled trials have demonstrated that treatment with coenzyme Q could be beneficial in patients with congestive heart failure, angina pectoris, cardiomyopathy, coronary artery disease and preservation of myocardium. Coenzyme Q10 is normally present in the low density lipoprotein cholesterol and inhibits its oxidation. It also regenerates vitamin E apart from its direct antioxidant activity. The dosage of coenzyme Q10 varies between 30 - 300mg/day in different indications. Epigastric discomfort, nausea, vomiting, diarrhoea and increase in SGOT and LDH are modest side effects of treatment.

Key Words:

Ubiquinone, coronary artery disease, hypertension, heart failure, cardiomyopathy.

Running Title:

Ubiquinone and Cardiovascular Disease.

Introduction:

Coenzyme Q10 (CoQ10) is also known as ubiquinone because it is present in every plant and animal cell[1-3]. It is a vitamin or vitamin like substance and is naturally present in foods. CoQ 10 is synthesised in all body tissues and to resolve the controversy on nomenclature it should be called antioxidant due to its free radical scavenging properties. The biosynthesis of CoQ10 from the amino acid tyrosine is a multistage process requiring at least eight vitamins and several trace elements[1-3].

Moor et al were the first[1] to identify CoQ10 in 1940 and Crane et al[4] in 1957 demonstrated that it played an important role as a redox carrier in the mammalian respiratory transport chain. In 1965, Yamamura et al[5] first used oral CoQ10 in the treatment of cardiovascular disease (CVD). Fruits, vegetables, legumes and nuts as well as animal, organ meat, soy oil, peanuts, sardines, mackerel etc. are important

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sources or CoQ10, however the amount from dietary sources is probably insufficient to produce the clinical effects observed with therapeutic doses of the nutrient.[1-3] The plasma level of CoQ10 is approximately two fold higher among vegetarians than in omnivores which indicates that a high intake of plant foods may preserve high CoQ10 levels[1-5].

Deficiency of Coenzyme Q10:

CoQ10 deficiency can exist which may be due to insufficient dietary CoQ10, impairment in CoQ10 biosynthesis, excessive utilization by the body or any combination of the three.[1-3] Most experts agree that the dominant source of CoQ10 in man is biosynthesis[1-3]. There is increased requirement of CoQ10 by body tissue in several diseases such as angina pectoris, congestive heart failure, mitral valve prolapse etc. (Table 1). It is possible that poor body stores or low dietary intake can predispose several of the diseases mentioned in the table 1 and CoQ10 supplementation may be protective.

TABLE 1.

Possible causes of coenzyme Q10 deficiency

Noncardiovascular conditions	Cardiovascular diseases
1. Persistent nausea, vomiting and diarrhoea.	1. Angina pectoris.
2. Cachexia.	2. Coronary artery disease.
3. Chronic malnutrition.	3. Congestive heart failure.
4. Suboptimal dietary intake of CoQ10	4. Hypertension.
5. Aging.	5. Cardiomyopathy.
6. Obesity	6. Mitral valve prolapse.
7. Acute shock states.	7. Revascularization.
8. Diabetes mellitus	
9. Cancer	
10. Immune deficiency	
11. Peridontal disease	
12. Muscular dystrophy.	
13. Drug therapy, e.g., statins, adriamycin, diuretics	
14. Excessive exertion.	
15. Hypermetabolism.	

Beneficial Effects:

CoQ10 is involved in the manufacture of ATP which is potentially useful in peventing cellular damage during myocardial ischaemia and reperfusion[1,2]. Coenzymes are cofactors upon which the comparatively large and complex enzymes depend for their function, CoQ10 is the coenzyme for at least three mitochondrial enzymes (complexes I, II and III) as well as enzymes in other parts of the cell. These enzymes concerned with oxidative phasphorylation pathway are essential for the production of the high energy phosphate ATP which is responsible for cell function[2].

The clinical benefits of CoQ10 are mainly due to its ability to improve energy production, antioxidant activity and membrane stabilizing properties [1-3]. These effects are most beneficial in the prevention and treatment of CVD and cancer. The antioxidant activity is limited to protection against lipid peroxidation. It has a sparing effect on vitamin E and works together with vitamin E in preventing damage to lipid membranes and plasma lipids.[6]. Treatment with CoQ10 may offer significant protection against atherosclerosis by preventing lipid peroxide formation and oxidation of low density lipoprotein cholesterol[7-9]. It may have some ability to maintain the integrity of myocardial calcium ion channels and potassium channels during ischaemic insults. CoQ10 might therefore activate potassium channels similar to nicorandil and modulate calcium channels resulting into decreased cellular calcium and improved cardiac integrity during ischaemia[10]. Decrease in the level of cytoplasmic calcium may be associated with hyperpolarisation of cell membrane which may mediate vasorelaxation.

Mechanism:

Recent studies indicate that overproduction of free radicals is the most important mechanism of cardiac damage during myocardial ischaemia and reperfusion[11,12]. Under normal conditions, 95-98% of molecular oxygen consumed by cells is reduced to water by the addition of four electrones. The remaining 2-5% are reduced by a univalent pathway. The addition of one, two or three electrons to oxygen, gives rise to the toxic and reactive intermediates. Thus, oxygen derived free radicals are produced in small concentrations even during normal oxidative metabolic reactions. Free radicals are molecules characterised with unpaired electron rendering it chemically active. If a free radical reacts with a nonradical species, another free radical is produced. This property of self perpetuation enables free radicals to initiate and perpetuate chain reactions. Superoxide anion (O_2), hydroxy radical and hydrogen peroxide are major

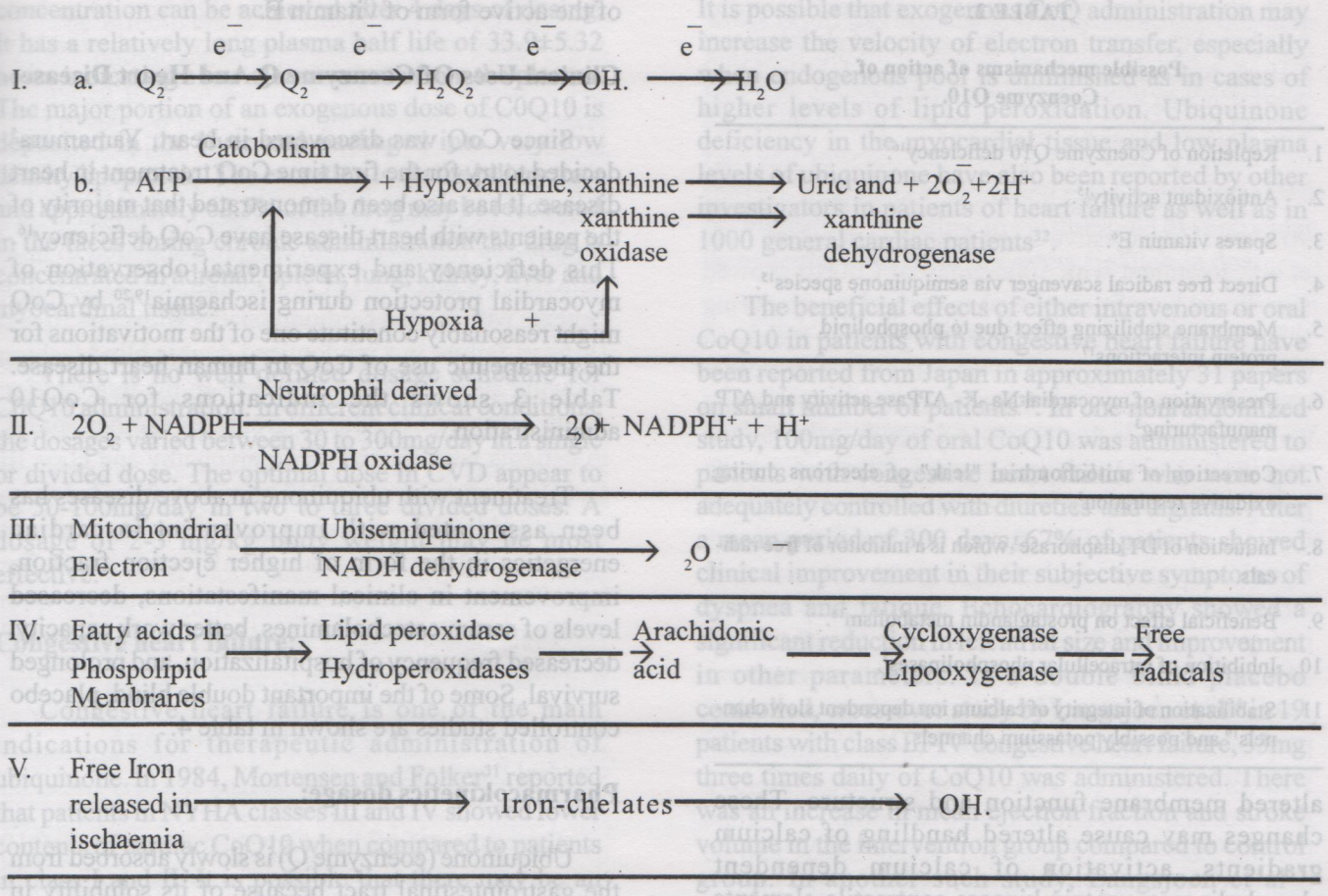

Figure:
Free radical generation during ischaemia.

species of free radicals which are produced during ischaemia[11,12].

During myocardial ischaemia, ATP is catabolized into adenosine, inosine and hypoxanthine (figure). In addition, xanthine dehydrogenase is selectively converted into xanthine oxidase via limited protolysis or by oxidation of thiol groups[13]. Oxygen combines with hypoxanthine in the presence of xanthine oxidase during postischaemic reperfusion of molecular oxygen which generates superoxide anion and ultimately other free radical species. Neutrophil is another potential source of free radical formation due to presence of membrane bound NADPH oxidase. This enzyme system produces superoxide radical. Mitochondria is the third source of free radical during myocardial ischaemia. Normally 2% of the oxygen consumed by electron transport produces partially reduced electrons. In this setting, 75% of the superoxide anion production appears to be due to ubisemiquinone. The electrons can leak out of the mitochondrion via pathways involving NADH dehydrogenase and ubisemiquinone[4]. Fatty acids present in the phospholipid membranes produce lipid peroxidase and hydroperoxidase that are activated during ischaemia which release arachidonic acid. Arachinonate in turn accelerate the production and perpetuation of free radical species via the cycloxygenase and lipooxygenase pathways. Release of iron in ischaemic tissue causes the production of iron chelates that may be active in catalyzing hydroxyl radical formation[1-3].

Free radicals have been implicated as mechanism of cellular injury during post-ischaemic reperfusion. Free radical peroxidize membrane phospholipids resulting in the liberation of lipid radicals, lipid alkoxy radicals, lipid peroxides and lipid hydroperoxides. Oxidation of sulphhydryl compound by hydroxyl radical may inactivate certain essential membrane proteins. The net result of free radical damage may be

TABLE 2.

Possible mechanisms of action of Coenzyme Q10.

1. Repletion of Coenzyme Q10 deficiency[16].
2. Antioxidant activity[15].
3. Spares vitamin E[6].
4. Direct free radical scavenger via semiquinone species[15].
5. Membrane stabilizing effect due to phospholipid protein interactions[17].
6. Preservation of myocardial Na -K- ATPase activity and ATP manufacturing[3].
7. Correction of mitochondrial "leak" of electrons during oxidative respiration[3].
8. Induction of DT diaphorase[3] which is a inhibitor of free radicals.
9. Beneficial effect on prostaglandin metabolism[18].
10. Inhibition of intracellular phospholipases[3].
11. Stabilization of integrity of calcium ion dependent slow channels[19] and possibly potassium channels.

altered membrane function and structure. These changes may cause altered handling of calcium gradients, activation of calcium dependent phospholipases, protein kinases contractile elements and accumulation of mitochondrial calcium leading to further cellular damage and necrosis. There is evidence that treatment with endogenous free radical scavengers superoxide dismutase and catalase can enhance cardiac function after ischaemia[14].

CoQ10 protects ischaemic tissue from reperfusion damage by its antioxidant and free radical scavenging activity[15]. The membrane stabilizing property is separate from its ability to neutralize free radicals. It seems that ubiquinone provides protection to myocardium as well as prevents oxidation of low density lipoprotein cholesterol. These basic mechanisms of action provide the rationale for the experimental and clinical use of coenzyme Q in cardiovascular diseases. These actions are similar to ACE-inhibitors and potassium channel activators. It is possible that there is "invivo" reduction of CoQ4 to its reduced Quinol form. This short, side chain Quinol might act as a radical scavenging antioxidant by donating phenolic hydrogen to peroxyl radicals[19,20]. The other possible antioxidant behaviour would be linked to the capability shown by ubiquinols to reduce the alpha-tocopheryl radical, thus allowing regeneration of the active form of vitamin E.

Clinical Uses Of Coenzyme Q And Heart Disease:

Since CoQ was discovered in heart, Yamamura[5] decided to try for the first time CoQ treatment in heart disease. It has also been demonstrated that majority of the patients with heart disease have CoQ deficiency[16]. This deficiency and experimental observation of myocardial protection during ischaemia[19,20] by CoQ might reasonably constitute one of the motivations for the therapeutic use of CoQ in human heart disease. Table 3 shows the indications for CoQ10 administration.

Treatment with ubiquinone in above diseases has been associated with improvement in cardiac energetics in the form of higher ejection fraction, improvement in clinical manifestations, decreased levels of serum catecholamines, better work capacity, decreased frequency of hospitalization, and prolonged survival. Some of the important double blind, placebo controlled studies are shown in table 4.

Pharmacokinetics dosage:

Ubiquinone (coenzyme Q) is slowly absorbed from the gastrointestinal tract because of its solubility in lipids. The mean plasma levels after a single 100mg oral dose of CoQ10 in human subjects is 1.004±0.37ug/ml.[1] The mean steady state level after thrice daily administration of 100mg has been estimated to be 5.4 ug/ml. Approximated 90% of the steady state

TABLE 3.

Therapeutic use of CoQ10

Cardiovascular diseases	Non-cardiovascular diseases
1. Congestive heart failure.	1. Muscular dystrophy.
2. Angina pectoris and AMI.	2. Peridontal disease.
3. Coronary artery disease.	3. Aging.
4. Toxin induced cardiomyopathy.	4. Cancer.
5. Myocardial preserving agent.	5. Diabetes mellitus
6. Hypertension.	6. Immune deficiency
7. Arrhythmias.	7. Cerebral ischaemia
8. Cardiomyopathy.	8. Physical performance.
9. Mitral valve prolapse.	
10. Potential imaging agent.	

AMI = Acute myocardial infarction.

concentration can be achieved after 4 days of dosing. It has a relatively long plasma half life of 33.9±5.32 hours indicating a low clearance rate from the plasma. The major portion of an exogenous dose of C0Q10 is deposited in the liver and packaged into very low density lipoprotein. The excretion is via the biliary tract and approximately 62.5% of the drug may be recovered in the faces during chronic administration the drug is concentrated in adrenal, spleen, lung, kidney, liver and myocardinal tissue.

There is no well defined dosage schedule for C0Q10 administration. In different clinical conditions, the dosages varied between 30 to 300mg/day in a single or divided dose. The optimal dose in CVD appear to be 50-100mg/day in two to three divided doses. A dosage of 2-3 mg/kg body weight may be most effective.

Congestive heart failure:

Congestive heart failure is one of the main indications for therapeutic administration of ubiquinone. In 1984, Mortensen and Folker[31] reported that patients in NYHA classes III and IV showed lower contents of cardiac CoQ10 when compared to patients in class I and II. It is possible that there may be an impairment of CoQ10 biosynthesis or accelerated catabolism or both causing a deficiency. Increased antioxidant commitment of CoQ may somehow lead to accelerated consumption and therefore deficiency.

TABLE 4.

Double blind placebo controlled studies on the role of CoQ10 in cardiovascular disease.

Year	Author	Disease
1985	Langsjoen et al[21]	Dilated cardiomyopathy
1985	Kamikawa et al[22]	Coronary artery disease
1985	Schardt et al[23]	" "
1987	Mazzola et al[24]	" "
1991	Rossi et al[25]	" "
1991	Wilson et al[26]	Coronary artery disease
1991	Bresolin et al[27]	Mitochondrial myopathy
1991	Paciaroni et al[18]	Heart failure
1992	Hofman-Bang et al[29]	Heart failure
1992	Trimarco et al[30]	Heart failure
1998	Singh et al [77]	Acute myocardial infarction

It is possible that exogenous CoQ administration may increase the velocity of electron transfer, especially when endogenous pool is diminished as in cases of higher levels of lipid peroxidation. Ubiquinone deficiency in the myocardial tissue and low plasma levels of ubiquinone have also been reported by other investigators in patients of heart failure as well as in 1000 general cardiac patients[32].

The beneficial effects of either intravenous or oral CoQ10 in patients with congestive heart failure have been reported from Japan in approximately 31 papers on small number of patients[33]. In one nonrandomized study, 100mg/day of oral CoQ10 was administered to patients with congestive heart failure who were not adequately controlled with diuretics and digitatis. After a mean period of 300 days, 67% of patients showed clinical improvement in their subjective symptoms of dyspnea and fatique. Echocardiography showed a significant reduction in left atrial size and improvement in other parameters. In a double blind placebo controlled, cross-over study by Langsjoen et al[34] in 19 patients with class III-IV congestive heart failure, 33mg three times daily of CoQ10 was administered. There was an increase in mean ejection fraction and stroke volume in the intervention group compared to control group. In another such study, Langsjoen et al[35] administered C0Q10, 33. 3mg thrice daily in 12 patients with documented class III-IV congestive heart failure for 12 weeks. There was a significant increase in stroke volume and ejection fraction in the CoQ10 group compared to control subjects.

The Scandinavian multicentre study by Hofman-Bang et al[29] in 79 patients was a double blind crossover trial in which majority (n=60) of the patients had class III heart failure. Intervention group showed improvement in physical performance and exercise capacity consistent with captopril-digoxin multicentre research trial. In another multicentre double blind trial[30] involving 33 centres, comprising 641 patients, 319 were administered CoQ10 and 322 placebo for 12 months. Although deaths were (16 vs 21) not significantly less, incidence of acute pulmonary oedema, arrhythmias, hospitalizations and incidence of class III and IV heart failure, were significantly lower in the CoQ10 group. Clinical benefit score (1-3) was much higher in the treatment group. In another double blind and controlled study[28] Ursini et al (Paciaroni group) treatment with CoQ10 was associated with significant reduction in catecholamines

with clinical improvement in the intervention group compared to control group in a group of elderly heart failure patient. However, a German double blind study[36] showed no benefit of CoQ10 in patients with well preserved cardiac function.

In a long-term randomized survival study among 90 class IV congestive heart failure patients by Judy et al[37], treatment with 100mg/day of CoQ10 showed significant benefit compared to control group during a follow up of 8 years. Both groups received conventional therapy of heart failure. There was a stable improvement with a reduction in heart failure and increased cardiac function (measured by electric impedance) in about a year among 78% of CoQ10 group. Improvement was rated within 40 days of CoQ10 administration. Survival after 8 years was significantly greater in the CoQ10 group with a survival incidence of 73% after one year. For this group survival percentages for 2-8 year were 65, 85, 50, 47, 36 and 24% respectively. In the control group, all patients were dead within 5 years. The 1 through 5-year survival percentages in this group were 54, 26, 16, 6 and 1% respectiverly.

In congestive heart failure due to CAD, there may be an ischaemia-reperfusion induced free indical stress in conjunction with higher serum catecholamines[38]. Higher sympathetic activity and catecholamines in heart failure may be associated with a deficiency of endogenosis antioxidants catalase and superoxide-dismutase, glutathione as well as antioxidant vitamins A, E and C and beta-carotene which further enhance the oxidative stress. These biochemical abnormalities may be associated with worsening of heart failure. In experimental animals an improved myocardial redox state with long term antioxidant therapy has been shown to modulate the development and progression of heart failure[39]. This study provides further proof to the rationale regarding the use of antioxidants in heart failure[38]. Carvedilol which is an antioxidant and betablocker has also been found to retard heart failure indicating that decrease in oxidative stress and sympathetic activity may be protective in heart failure[38].

Cardiomyopathy:

It is not clear whether CoQ10 deficiency is a risk factor of cardiomyopathy or the state of cardiomyopathy is the cause of the deficiency. In one study[40], tissue levels of coenzyme Q10 from 43 patients with documented cardiomyopathy were obtained via endomyocardial biopsy technique. Tissue level of CoQ10 was significantly lower among NYHA class IV subjects compared to class 1 and 2 subjects. Frustaci et al[41] reported that a greater deficiency of CoQ10 at baseline in dilated cardiomyopathy showed better response to treatment with CoQ10 compared to mild deficiency. Langsjoen et al[21] administered CoQ10 in patients with dilated cardiomyopathy with class III and IV heart failure in a randomized double blind fashion showing significant improvement in the intervention group compared to control group. In another study[35] in patients with dilated cardiomyopathy and class III and IV heart failure, CoQ10 administration led to an increased blood levels with simultaneous improvement in clinical status and myocardial function. Similar benefit was observed among 126 patients with cardiomyopathy on treatment with CoQ10 for 42 months.

Myocardial Protection, Intervention and Cardial Surgery:

Experimental studies suggested that prior CoQ10 therapy provides protection against ischaemic reperfusion[1-3]. Naylar (1980)[42] working with a rabbit heart model of ischaemia and reperfusion, showed for the first time a role of CoQ10 in preserving ischaemic myocardium. She reported that myocardium pretreated with CoQ10 was relatively protected against both structural and functional changes induced by ischaemia and reperfusion. The animals pretreated with CoQ10 were able to maintain oxidative phosphorylation and cellular ATP generating capacity and showed that cellular and mitochondrial calcium overload was prevented by pretreatment with CoQ10. The clinical and metabolic beneficial effects were similar in magnitude to those seen with propranolol and verapamil[1]. CoQ10 has been demonstrated to protect both Ca dependent and Na-K dependent ATPase activity in adult mongrel dogs and total ATP content in experiments. Nagai et al[43] reported that both damage secondary to reperfusion and post reperfusion arrhythmias can be inhibited by pretreatment of animals with CoQ10. In one experiment[44] with isolated perfused rat heart, Ohhara et al[44] showed that CoQ10 facilitated recovery of mechanical performance following global ischaemia.

The effectiveness of CoQ10 in preventing low cardiac output states following cardiac surgery was compared in a randomized study in humans[45]. The CoQ10 treated patients showed a significantly lower incidence of low cardiac output states postoperatively compared to controls. In another study[46], CoQ10 was administered to patients just before coronary artery bypass surgery compared to control group. The CoQ10 treated patients had significantly higher left ventricular stroke work indices, lower requirement for inotropic support and significantly lower levels of serum creatine phosphokinase-MB in the postoperative state. In a more recent study, Judy et al[47] demonstrated myocardial preservation by prior treatment with CoQ10 for 15 days before heart surgery and after 30 days treatment after the surgery. The CoQ10 group showed optimal blood and tissue CoQ10 and tissue ATP levels, improvement in cardiac pumping and ijection fraction as well as uncomplicated and short recovery period compared to placebo treated group. It is possible that CoQ10 might have a role as an ischaemia modifier in several cardiac conditions including unstable angina, acute myocardial infarction, thrombolysis and coronary artery bypass surgery and possibly heart transplantation. There is a need to examine the effect of parenteral CoQ10 therapy before thrombolysis (mechanical or fibrinolytic) in patients with acute myocardial infarction to confirm that it can protect against ischaemia and reperfusion induced free radical damage.

Cardiac Arrhythmias:

One experimental study[48] with mitochondria isolated from the heart after 40min occlusion of the coronary artery showed higher levels of hydroxyl radicals in conjunction with lower levels of coenzyme Q10. Mitochondrial free radicals were detected by election spin resonance. The effect of CoQ10 pretreatment was evident primarily in relation to oxidative damage. There was a great increase in malondialdehyde production upon reperfusion in placebo group compared to CoQ10 group. In experimental coronary artery ischaemia, pretreatment with CoQ10 increased the ventricular fibrillation threshold while minimizing the impairment in contractility and myocardial stunning[49]. The antiarrhythmic effect of CoQ10 has been studied in several experiments. Arta et al[50] showed that treatment with CoQ10 was associated with prolongation of action potential duration in dog right ventricular papillary muscles. Experiment[51] in single cultured myocardial cell showed that CoQ10 increased the regular beating rate and lowered the irregular beating frequency of the cell. Sugiyama et al[52] found that CoQ10 decreased the magnitude of decline in the threshold of ventricular tachycardia after coronary artery ligation in dog.

Clinical studies[53-55] on the role of CoQ10 in patients with ventricular ectopic activity indicate that 20-25% of patients respond to treatment with this agent. These studies also showed a consistent effect of CoQ in shortening the QT interval including QTc. CoQ10 may have similar effect on QT interval in patients receiving psychotropic agents.

Angina Pectoris and Coronary Artery Disease:

Since CoQ10 can protect against ischaemia, it is possible that it can be a potential antianginal drug indicating its use in coronary artery disease (CAD). In a controlled trial[56] intravenous CoQ10, 1.5mg/kg once daily, for 7 days was administered in 18 patients with chronic stable angina. The mean exercise time showed significant increase compared to placebo treatment from a baseline of 4.55±2.03 to 7.15±2.5 minutes. Heart rate, blood pressure, and double product showed little change.

At least five double blind, controlled intervention trials have been published to demonstrate the role of CoQ10 in CAD[22-26]. Kamikawa et al[22] administered oral CoQ10 (150mg/day in three daily doses) or placebo for 4 weeks in 12 patients with chronic stable angina. This was followed by a crossover to the opposing treatment regimen for another 4 weeks. Exercise time and time to onset of 1mm electrocardiographic ST-depression were significantly increased in the CoQ10 group compared to placebo group. (Table 5). Schardt et al[23] compared the effects of 600mg/day of oral CoQ10 with placebo and the combination of pindolol (7.5 mg/day) and isosobidedinitrate (30mg/day) in 15 patients with chronic stable angina. Treatment with CoQ10 was associated with a significant reduction in cumulative exercise-induced ST-segment depression compared to placebo but no difference was noted compared to conventional antianginal drugs. There was a significant reduction in exercise systolic blood

pressure in the CoQ10 group than placebo. In a multicentre study[26], the effect of CoQ10 in doses of 150 or 300mg/day was compared with placebo in 37 patients on exercise duration in stable angina at 10 different centres. CoQ10 monotherapy caused an increase in exercise duration to onset of angina of 70 seconds in the 300mg group and 65 in the 150 mg group at end of first week and of 140 and 127 seconds respectively by week 4. There was a 60% decrease in the frequency of anginal attacks in the 150mg group. In post infarction patients[25], treatment with CoQ10 caused a significant beneficial effect on work capacity and significantly lower level of malondialdehyde in the treatment group compared to placebo. In one 58 years old patient with diabetes mellitus and unstable angina, addition of CoQ10 (60mg/day) to treatment with nitrates and calcium blockers was associated with exercise tolerance and relief in angina within 2 weeks, although no response was observed during the last 4 weeks with conventional drugs. (unpublished, RBS).

TABLE 5

Effect of Coenzyme Q10 in patients with unstable angina.

Data (n=12)	Baseline	Coenzyme Q10	Placebo
Frequency of anginal attacks/ 2 weeks	4.6 (4.1)	2.5 (3.3)	5.3 (4.9)
Nitroglycerin consumption/ 2 weeks	2.8 (2.8)	1.3 (1.7)	2.6 (2.8)
Exercise time (Sec)	340 (126)	406 (114)	345 (102)*
Time to onset of 1mm ECG ST-depression (Sec)	205 (90)	284 (104)	196(76)**

* = $p<0.05$, ** = $p<0.01$. Values are mean (SD).

The exact mechanism of improved exercise capacity after CoQ10 therapy is not exactly known. It is possible that CoQ10 has beneficial effect on oxidative phosphorylation, enhances resynthesis of ATP, a direct membrane protection or reduction in free radical stress. These actions are different than those of conventional antianginal drugs betablockers, calcium antagonists and nitrates. Currently CoQ10 is being extensively studied in the developed countries for its antianginal efficiency. The drug do not have any appreciable hemodynamic effect.

Hypertension:

The role of CoQ10 in decreasing blood pressure is known[57] since 1972. It has been examined in several studies on animals with induced arterial hypertension. Yamagami et al[58] in 1977 found CoQ10 deficiency in 29 patients with hypertension and treatment with CoQ10 (1-2mg/kg/day) caused decrease in blood pressure. Earlier in a pilot study, he administered 30-45mg/day of CoQ10 in 17 patients of hypertension for 2-16 weeks showing a beneficial effect only in 4 patients. In one randomized, double blind and controlled study by Yamagami et al[50], 20 patients having low serum CoQ10 levels and low succinate dehydrogenase CoQ reductase, actively were administered either 33.3mg CoQ10 three times daily or placebo for 12 weeks. Treatment with CoQ10 was associated with significant decrease in systolic (167±2.6 vs 148±4.4 mmHg) and diastolic (97±1.8 vs 91±3.7 mmHg) blood pressures in the intervention group compared to baseline blood pressures without such changes in the control group. Montaldo et al[60] administered CoQ10, 100mg/day for 3 months to 15 patients of hypertension. There was a significant reduction in blood pressures both at rest and during exercise, together with a significant improvement in myocardial stroke work index. Digiesi et al[61,62] also studied the role of CoQ10 in hypertension and reported a decrease in total peripheral resistance which may be due to improvement in arteriolar smooth muscle cell metabolism. In a recent study by Langsjoen et al[63] in 109 patients with known essential hypertension CoQ10 (225mg/day average) was administered to achieve serum level of 2μg/ml, in conjunction with anti-hypertensive drugs. There was a need to withdraw one to three drugs in 51% of patients. The decrease in systolic blood pressure was from 159 to 147 mmHg, mean and in diastolic blood pressure from 94 to 85mmHg. A further study[28] showed that CoQ10 causes a significant decrease in serum catecholamines and possibly reduces peripheral vascular resistance. The available data indicate that a double blind randomized study should be conducted with higher doses (100-

200mg/day) of CoQ10 with a follow up of at least 12 weeks to demonstrate its role in decreasing blood pressure.

Mitral Valve Prolapse:

There is evidence that mitral valve prolapse may be associated with CoQ10 deficiency[64]. Clinical studies suggest that CoQ10 may improve cardiac performance under exercise conditions in patients with mitral valve prolapse[64].

Adriamycin Myocardial Toxicity:

Adriamycin, an anthracycline and mixed quinoid and hydroquinoid compound may have inhibition effects on CoQ10 enzyme systems[65] Kishi et al (1976)[68] reported that repletion with CoQ10 can prevent the inhibition of CoQ10 enzymes in mitochondrial preparations. In several other experimental studies[1,67]. The role of exogenous CoQ10 in preventing adriamycin toxicity was corroborated.

Clinical studies[68] also showed a beneficial effects on systolic time intervals of pretreatment with CoQ10 (a manifestation of adriamycin toxicity) in cancer patients. In a prospective study using impedence cardiography, it has been reported that cancer patients receiving CoQ10 together with adriamycin exhibited less reduction in ijection fraction[69]. In a randomized and controlled study[70] in 20 patients with cancer, 10 were supplemented with 200mg/day of CoQ10 for the duration of treatment with anthracyclins. Echocardiographic monitoring showed protective effects on the left ventricular contractile function in the form of less decrease in ijection fraction and of shortening fraction in the CoQ10 group compared to control subjects. It is possible that CoQ10 therapy causes repletion of a CoQ10 deficiency induced by adriamycin and inhibits adriamycin induced lipid peroxidation and free radical generation[68].

Plasma Lipoproteins:

In one invitro experiment[7], it has been

TABLE 6.

Coenzyme Q therapy in refractory heart disease.

Disease	Age	Drug therapy	Duration	Coenzyme Q10	FBG (mg/dl)	
					Before	After
1. Refractory Ventricular ectopics CAD, diabetes	47 male (n=1)	Lignocaine Dysopiramide	4 weeks	20mg Thrice daily x 2wks	150	132
2. Refractory angina, diabetes	58 male (n=1)	Nitrates diltiazem	7 weeks	20mg Thrice daily x 3wks	148	138
3. Refractory heart failure, diabetes, CAD	46 male (n=1)	digoxin, Nitrates, enalepril maliate furosemide	6 weeks	20mg Thrice daily x 3 wks	190	156
4. Refractory heart failure diabetes, CAD	52 female (n=1)	digoxin nitrate enalepril maliate furosemide	5 weeks	20mg Thrice daily x 2wks	164	145
5. Refractory cardiogenic shock, CAD, diabetes	54 male (n=1)	Dopamine, dobutamine, hydrocortisone henvisuccinate	48 hours	20mg four times daily x 1wk.	138	135

CAD = Coronary artery disease. FBG = Fasting blood glucose.

demonstrated that following exposure to free radical source (Azo compounds) low density lipoproteins (LDL) deployed their antioxidant reserve which were consumed while inhibiting the oxidative attack[7]. Ascorbic acid was first to intervene, followed by reduced CoQ10. When LDL depleted of ascorbic acid were exposed to free radical source, peroxidation was remained under control as long as some ubiquinol was present. However when ubiquinol was completely oxidized, lipid peroxidation really started despite 95% of vitamin E and 80% of initial carotenoid content were still present. The findings suggested that ubiquinol as an antioxidant may be more efficient than tocopherol and carotenoids in preventing the oxidation of LDL. It is also possible that ubiquinol enhances the antioxidant activity of vitamin E and carotenoids. Supplementation of LDL in vitro with ascorbic acid or ubiquinol caused significant decrease in the peroxidizability of LDL induced by oxidants such as copper iron treatment[8].

A double blind controlled study[7] in patients with hypercholesterolemia showed that treatment with HMGCoA reductase (lovastatin) was associated with significantly lower plasma level of CoQ10 compared to placebo. The decrease in CoQ10 appears to be due to the fact that cholesterol and CoQ10 share the same biosynthetic pathway. These findings were confirmed in a crossover trial with CoQ10 and HMGCoA inhibitors.[72,73]. This study showed a decrease in CoQ10 in plasma as well as in platelets which was prevented by concomitant administration of CoQ10. However long term treatment with HMGCoA reductase inhibitors has been associated with significant reduction in cardiac events as well as in the regression of atherosclerosis[74]. In one experimental study, Singh et al[75] demonstrated that lovastatin has a modest antioxidant activity which may be similar to fluvastatin. It is possible that despite a reduction in CoQ10 induced by statins, oxidation of LDL is inhibited by the statins resulting into no serious adverse effect of CoQ10 deficiency. However it is likely that treatment of hypercholesterolemia with HMGCoA reductase inhibitors in conjunction with CoQ10 may provide greater benefit in the regression of coronary atherosclerosis and prevention of cardiac events. This assumption is quite possible as higher LDL/CoQ10 ratio was significantly associated with CAD[76]. It seems that decrease in this ratio either by increasing CoQ10 level or by decreasing the LDL level or by both may be protective in the prevention of CAD.

The newly discovered presence of CoQ10 in cellular membranes other than mitochondrial ones and in plasma lipoproteins suggest that CoQ10 can decrease oxidation of LDL resulting into a possible decrease in atherosclerosis.

Miscellaneous:

In several miscellaneous conditions such as diabetes, stroke, immunodeficiency, muscular dystrophy and myopathy, treatment with CoQ10 may be protective[1-3]. We have administered CoQ10 in refractory heart failure (n=2) and cardiogenic shock (n=1) and refractory angina (n=1) and ectopics (n=1) showing beneficial effects in all the 5 cases. All patients who also had associated (Table 6) diabetes (n=3) showed improvement in glucose levels. Higher tissue levels of CoQ10 may be seen during thyroid harmone treatment, cold adaptation and exercise due to increased biosynthesis as an adaptive response to oxidative stress. (Table 7) Table 6: Coenzyme Q therapy in refractory heart disease.

TABLE 7.

Age related changes in ubiquinone content in human organs*

Organ	1-3 days	0.7-2 years	19-21 years	39-41 years	77-81 years
Heart	36.7	78.5	110	75	47
Kidney	17.4	53.4	98	71	64
Liver	13	45	61	58	51
Pancreas	9	38	21	19	6.5
Spleen	21	80	33	29	13
Adrenal	17.5	58	16	12	8.5
Lung	2.2	6.4	6	6.5	3

Adverse Manifestations:

There are no major adverse effects[1-3] of CoQ10 administration in pharmacological dosages of 30-300mg/day. These side effects attributed to CoQ10 therapy may be mainly gastro-intestinal (Table 8). Asymptomatic elevations of lactic dehydnogenase (LDH) and serum glutamic-oxaltransterase (SGOT) can occur with higher doses above 300mg/day of CoQ10. Oral hypoglycemic agents and HMGCoA

reductase inhibitors[71] and also possibly diuretics may enhance the requirement of CoQ10 and need supplementation. Further studies using higher doses of CoQ10 in the treatment and long term administration would be necessary to find out the safety of this drug.

TABLE 8.

Adverse effects of Coenzyme Q10

	Effects	%
1.	Nausea	0.16%
2.	Decreased appetite	0.23
3.	Epigastric discomfort	039
4.	Vomiting	Rare
5.	Diahrroea	0.12
6.	Rise in LDH	Rare
7.	Rise in SGOT	Rare

Conclusion:

CoQ10 is still in the investigational stages. It is sold as a health product in United States and its therapeutic uses can not be patented, hence drug industry is not interested in research on CoQ10. The most intriguing property of CoQ10 is its potential ability to protect and preserve ischaemic myocardium. However no randomized controlled intervention trial exist on its use in decreasing myocardial infarction size and prevention of complications in patients with acute myocardial infarction. In acute myocardial infarction, ischaemic reperfusion injury is an important determinant of complications hence CoQ10 should be administered as soon as possible on suspicion of infarction, preferably intravenously, before the thrombolytic agents to achieve maximum protection. Singh et al appear to be possibly the first to provide such evidence of their randomized trial in 50 patients with suspected acute myocardial infarction[77].

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