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Coenzyme Q10 and Utility in Heart Failure: Just Another Supplement?

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Abstract Heart failure affects 5.1 million people in the USA annually. It accounts for a frequent cause of hospitalizations and disability. Patients with congestive heart failure have lower plasma levels of CoQ10, which is an independent predictor of mortality in this patient population. It has been hypothesized that a deficiency of CoQ10 can play a role in the development and worsening of heart failure, and that oral supplementation can possibly improve symptoms and survival in these patients. Based on previous small studies and meta-analyses, the use of CoQ10 in heart failure suggested an improvement ejection fraction, stroke volume, cardiac output, and cardiac index with CoQ10 supplementation, however most of these small studies appeared to be underpowered to result in any significant data. The results of the recent Q-SYMBIO trial demonstrated an improvement in heart failure symptoms with a significant reduction in major adverse cardiovascular events and mortality.

Keywords Heart failure · Coenzyme Q10 · Ubiquinone · Ubiquinol

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Introduction

Heart failure affects 5.1 million people in the USA annually and it is associated with approximately 275,000 deaths per year [1]. Almost 50 % of people who develop heart failure die within the first 5 years of this diagnosis and it is a frequent cause of hospitalizations and disability amounting to total costs of an estimated US$32 billion annually [1].

In the last 30 years, there have been major improvements in the therapeutic management of heart failure; however, mortality rates continue to exceed 10 % per year [1]. Recently, long-term therapy with coenzyme Q10 (CoQ10) has been shown to improve heart failure symptoms, reduce major adverse cardiovascular events, and mortality and to be safe and well tolerated [2]. This review will summarize the literature related to CoQ10 in the treatment of heart failure.

Coenzyme Q10

Pathobiology

CoQ10 exists in two different forms: a reduced form, as ubiquinol (CoQ10H2), and as an oxidized form, ubiquinone (CoQ10) [3]. It is endogenously produced, and converts between the two forms, as the reduced or antioxidant form and as the oxidized form, as part of normal cellular enzyme functions [3]. It is a lipid-soluble molecule that uses lipoprotein-mediated transport for circulation, and is located in the lipid mitochondrial membranes, to protect the membranes from damage by free radicals [3]. It correlates with total and low density lipoprotein cholesterol levels and it acts as a free radical scavenger.

CoQ10 is found in the mitochondria of nearly every cell in the body; however it is most highly concentrated in the mitochondria of the heart, liver, and kidneys. Its

main role is to participate in aerobic cellular respiration to create adenosine triphosphate (ATP) for the production of energy. It is an essential cofactor in oxidative phosphorylation in the mitochondria. It does this by mediating electron transfer in the electron transport chain, by shuttling them from complex I and II to complex III in the mitochondrial respiratory chain in order to generate ATP [3]. Ninety-five percent of the human body energy is generated in this way.

CoQ10 also works by having direct antioxidant effects and preventing membrane oxidation and lipid peroxidation, stabilizes LDL, and promotes recycling of alpha-tocopherol. This occurs when ubiquinone acts as a cofactor to produce ATP and is reduced to ubiquinol. Ubiquinol then interacts with free radicals and is oxidized back to ubiquinone [3].

Coenzyme Q10 levels are highest in the first 20 years of life and the levels decline as the subject ages. About 25 % can be supplied from the diet and it is present in certain foods especially meat, fish, and vegetable oils [3].

Coenzyme Q10 in Heart Failure

Coenzyme Q10 (CoQ10) or ubiquinone, is a coenzyme that is endogenously produced [2]. CoQ10 functions as an electron carrier in the mitochondria and is essential for the production of the majority of the cellular energy in the human body [2]. CoQ10 was first discovered and isolated, in 1957, in beef hearts at the University of Wisconsin Enzyme Institute [3]. In 1961, Peter Mitchel found it to be an important part of the electron transport chain and in the production of energy [4].

In the early 1970s, it was demonstrated by Folkers et al. that patients with congestive heart failure had lower levels of CoQ10 in their blood and cardiac tissue [5]. In a follow-up study, Folkers et al. demonstrated that myocardial CoQ10 levels declined as heart failure worsens, with the largest deficiency of CoQ10 levels in patients with NYHA class IV symptoms. [6]. It is also known that the low levels of CoQ10 in patients with heart failure are an independent predictor of mortality in these patients [7]. In addition, CoQ10 deficiency can play a role in the development and worsening of heart failure [2].

CoQ10 as a therapeutic agent may have a beneficial effect in patients with heart failure by three different actions. First, it increases ATP generation and cellular energy by mediating electron transfer in the electron transport chain. Second, by reducing oxidative stress, a well-known marker of mortality in heart failure, and by preventing membrane oxidation and lipid peroxidation [8, 9] Third, by stabilizing calcium-dependent ion channels in the myocardium thus enhancing ATP synthesis [2, 10].

Coenzyme Q10

Clinical Trials (Table 1)

Randomized Controlled Studies In 1980, Langsjoen and Folkers performed the first US trial of CoQ10 in the treatment of heart failure [11, 12]. Subsequently, they evaluated its long-term effects in 143 patients over a 6-year period. The data demonstrated that the overall mortality was one third of expected with CoQ10 and that there was an improvement in cardiac function on the active treatment [11, 13]. Other studies such as the trial by Oda et al. showed that there was a normalization of cardiac function in 40 patients with mitral valve prolapse who took 3.1–3.4 mg/kg day of CoQ10 [14]. Rossi et al. [15] followed 20 patients with ischemic cardiomyopathy for 3 months in a double-blinded fashion and demonstrated that patients on CoQ10 therapy had improvements in ejection fraction and exercise tolerance. In addition, Poggesi et al. confirm that patients on coenzyme Q10 with ischemic and dilated cardiomyopathy had an improvement in ejection fraction and exercise tolerance [16]. Other studies confirmed improvements in cardiac performance with the use of coenzyme Q10 in heart failure and also demonstrated an improvement in quality of life. Some of these studies demonstrated a minimal improvement in survival [17–25].

The largest randomized controlled study by Morisco et al. followed 641 patients with heart failure, NYHA class III or IV symptoms, for 1 year and demonstrated that patients taking supplemental CoQ10 had a 50 % reduction in hospitalizations although there was no improvement in mortality [26].

Conversely, there are three other studies, which did not show any benefit in cardiac function or exercise tolerance in patients treated with coenzyme Q10 [27–29]. These studies were found to have small sample sizes, the doses of coenzyme Q10 were lower, and the severity and duration of heart failure was not clear.

The majority of these trials confirmed that patients with heart failure had an improvement in hemodynamic parameters such as ejection fraction, and cardiac output with CoQ10 supplementation. In addition, CoQ10 improved functional capacity and quality of life. However the sample sizes in these trials were relatively small and most of these trials were underpowered to address major clinical endpoints.

Meta-analyses

In order to overcome these issues, three meta-analyses confirmed that there was an improvement in ejection fraction,

Table 1 Table of trials of coenzyme Q10 in heart failure

Study	Year	Patient number	Dosage used	Outcome
Q-SYMBIO [38, 39]	2013–2014	420	300 mg daily	Improved survival, clinical improvement
Kocharian[a] [33]	2009	38	2 mg/kg	Improved EF in children
Adarsh[a] [34]	2008	46	200 mg daily	Improved NYHA, 6mw, diastolic dysfunction in hypertrophic cardiomyopathy
Berman[a] [35]	2004	32	60 mg daily	Improved NYHA, 6mw, clinical improvement
Keogh[a] [36]	2003	39	150 mg daily	Improved NYHA, 6mw, clinical improvement
Khatta[a] [29]	2000	55	200 mg daily	No improvement
Munkholm[a] [19]	1999	22	200 mg daily	Improved EF, NYHA
Watson [22]	1999	30	100 mg daily	No improvement
Hofman-Bang [18]	1995	79	100 mg daily	Improved EF, quality of life
Morisco [26]	1994	6	150 mg daily	Improved EF, CO, and SV
Morisco[a] [20]	1993	641	2 mg/kg daily	Improved NYHA, fewer hospitalizations and less major card events
Rengo [17]	1993	60	100 mg daily	Improved EF, quality of life
Permanetter [27]	1992	25	100 mg daily	No improvement
Rossi et al. [15]	1991	20	200 mg daily	Improved EF
Pogessi et al. [16]	1991	20	100 mg daily	Improved EF
Judy et al. [21]	1991	180	100 mg daily	Improved survival
Langsjoen et al. [22]	1990	143	100 mg daily	improved EF, NYHA, improved survival
Oda et al. [14]	1990	40	3.1–3.4 mg/kg daily	Improved cardiac function
Judy et al. [23]	1986	14	100 mg daily	Improved EF, CO
VanFraechem et al. [24]	1986	15	100 mg daily	Improved EF, CO, and SV
Schneeberger et al [25]	1986	12	100 mg daily	Improved EF, CO
Langsjoen et al. [12]	1985	19	100 mg daily	Improved EF, clinical improvement

[a] Trials included in the Cochrane Database Review

stroke volume, cardiac output, and cardiac index in patients with heart failure on CoQ10 treatment. The first meta-analysis by Soja and Mortenson reviewed eight double-blinded placebo-controlled trials in patients with heart failure and demonstrated that compared to the placebo group, patients on coenzyme Q10, achieved a better ejection fraction, stroke volume, cardiac output, cardiac index, and end diastolic volume [30]. In another meta-analysis of 11 studies with coenzyme Q10 by Sander et al., they were able to show similar results with an improvement in ejection fraction (3.7 %), cardiac output (0.28 L/min), stroke volume, and cardiac index. [31] Moreover, the authors demonstrated that that ejection fraction improved by 6.74 % in patients without angiotensin-converting enzyme inhibitor (ACEi) therapy compared to 1.16 % change in patients with angiotensin-converting enzyme inhibitors [31].

Fotino et al. also showed similar results in a meta-analysis where CoQ10 supplementation improved ejection fraction (3.7 %) and cardiac output in patients with systolic heart failure [32]. A subgroup analysis revealed an improvement in ejection fraction by 4.8 % in patients with ejection fractions of greater than 30 % compared to no change in patients with an ejection fraction less than 30 % [32].

The data of these meta-analyses suggested that the utilization of coenzyme Q10 produces functional improvement and improved hemodynamic parameters in patients with heart failure. The effects of coenzyme Q10 on mortality were not clearly demonstrated.

Systematic Review

In 2014, a Cochrane systematic review evaluated seven randomized controlled trials [19, 20, 29, 33–36], with a total of 914 patients [10] that compared CoQ10 with placebo in patients with heart failure and demonstrated that there was no effect on total mortality.

Thus, although CoQ10 appeared to be safe based on the previous small studies and meta-analyses that appeared underpowered, the ACC/AHA did not recommend CoQ10 in the 2013 guidelines [37].

Q-SYMBIO Trial

In order to clarify the effects of coenzyme Q10 on mortality and other endpoints, the Q-SYMBIO trial was designed. The Q-SYMBIO trial is a prospective, randomized, double-

blinded, placebo-controlled, multicenter trial of CoQ10 as an adjunctive treatment for chronic heart failure. It included 420 patients with moderate to severe CHF on standard therapy, who were assigned to receive, for a 2-year period, CoQ10 100 mg three times daily ($n = 202$) or placebo ($n = 218$). Changes in symptoms, biomarkers, long-term outcomes, and major adverse cardiovascular events (MACE) were recorded [38, 39].

No significant differences were observed for secondary end points (NYHA functional class, visual analogue scale score for dyspnea, fatigue, and improvement in symptoms, N-terminal pro-brain natriuretic polypeptide (NT-proBNP) and 6-min walk test) between two groups at 16 weeks. However, at week 106 (intention to treat), there was a significant reduction in MACE (defined as a hospitalization due to worsening heart failure, death from a cardiovascular cause, urgent heart transplantation, or artificial mechanical support) in the CoQ10 group. In addition, NYHA class improved by one class and serum NT-proBNP decreased from 1137 to 881 pg/mL. There was also a decrease in the rates of cardiovascular mortality (9 vs 16 %), all-cause mortality (10 vs 18 %), and hospitalizations. The number of adverse events tended to be less in the CoQ10 group. In summary, Q-SYMBIO demonstrated that the long-term supplementation of CoQ10 in patients with heart failure seems safe and not only improves symptoms but reduces MACEs and decreases mortality [38, 39].

Coenzyme Q10

Supplements and Interaction With Medical Therapy

The difficulty in achieving therapeutic levels of coenzyme Q10 is that this compound is fat soluble therefore intestinal absorption can be difficult, with as much as 50 % being excreted. The absorption of coenzyme Q10 in patients with heart failure is more difficult because of intestinal edema and congestion [40, 41]. Therefore, having a formulation that allows for better bioavailability is important. Bioavailability is the lowest in the powder form, increases as an oil emulsion, and is best as solubilized compounds and nanoparticles [2]. Higher doses of CoQ10 are associated with higher serum levels, however absorption is non-linear, so higher doses are more effective if they are divided into multiple doses [3].

The majority of supplements of coenzyme Q10 are in the oxidized form, ubiquinone, which has been in the majority of the clinical trials. Although the more expensive formulation ubiquinol is now available in pill form, it should not make a difference to prescribe either one, since ubiquinone is converted to ubiquinol after absorption. However, one study demonstrated that ubiquinol was better absorbed into the bloodstream and patients have higher serum levels [42, 43].

A serum blood levels of 3.5 μg/mL or greater is needed for improvement of cardiac function according to the clinical trials [42] There are no serious adverse effects with coenzyme Q10 except for mild gastrointestinal discomfort [43].

Recommended doses of CoQ10 are the following:

Congestive heart failure (CHF): 300 mg/day in 2–3 divided doses [8, 44]
Coronary artery disease: 300 mg daily in 2–3 divided doses [45]
Hypertension: 120 mg daily in two divided doses [46, 47]
Statin user: 100–200 mg/day although not definitive evidence [48–50]

Statins and beta-blockers are frequent agents utilized in patients with heart failure that have been shown to decrease CoQ10 levels by inhibiting the mevalonate pathway. Statins can reduce blood serum levels of CoQ10 by almost much as 40 % [50]. It has been suggested that fatigue, muscle pain, and weakness with statin use are related to a deficiency in coenzyme Q10. Interestingly, in patients with normal cardiac function, who received 20 mg of atorvastatin, 70 % developed diastolic dysfunction that was reversible with CoQ10 supplementation [51].

Conclusion

Currently, Europe, Russia, the USA, and Japan make up 85 % of the total consumption of CoQ10 supplementation. In Japan, CoQ10 was approved as treatment for heart failure in 1974 [29]. In 1982, it became one of the top five medications used in Japan [52]. The use of coenzyme Q10 is not advocated in the American College of Cardiology/American Heart Association HF guidelines from 2013.

The results of the recent Q-SYMBIO trial demonstrate that the utilization of coenzyme Q10 in patients with heart failure improves symptoms and is associated with a significant reduction in major adverse cardiovascular events and mortality without any major side effects [38, 39]. In summary, the evidence suggests that supplemental CoQ10 may be a useful option for the management of patients with heart failure.

Compliance with Ethical Standards

Conflict of Interest Sylvia Oleck and Hector O Ventura have no disclosures.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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