Coenzyme Q₁₀ as an Adjunctive in the Treatment of Chronic Congestive Heart Failure

CLAES HOFMAN-BANG, MD,* NINA REHNQVIST, MD, PhD,† KARL SWEDBERG, MD, PhD,‡ INGELA WIKLUND, MSc, PhD,§ HANS ÅSTRÖM, MD, PhD,* FOR THE Q₁₀ STUDY GROUP§

Stockholm, Danderyd, Gothenburg, Sweden

Abstract: Seventy-nine patients with stable chronic congestive heart failure were randomized into a double-blind, crossover placebo controlled study with 3-month treatment periods, where either 100 mg coenzyme Q₁₀ (CoQ₁₀) or placebo was added to conventional therapy. Mean patient age was 61 ± 10 years, ejection fraction at rest was 22% ± 10%, and maximal exercise tolerance was 91 ± 30 W. The follow-up examinations included ejection fraction (primary objective), exercise test, and quality of life questions. Ejection fraction at rest, during a slight volume load, and during a submaximal supine exercise increased slightly compared with placebo: 24% ± 12% versus 23% ± 12% (NS), 25% ± 13% versus 23% ± 12% (P < .05), and 23% ± 11% versus 22% ± 11% (NS). Maximal exercise capacity increased from 94 ± 31 W during the placebo period to 100 ± 34 W during the CoQ₁₀ period (P < .05). Total score for the quality of life assessment increased significantly from 107 ± 23 during the placebo period to 113 ± 22 during the CoQ₁₀ period (P < .05). The results indicate that oral long-term treatment with 100 mg CoQ₁₀ in patients with congestive heart failure only slightly improves maximal exercise capacity and the quality of life and that the clinical importance of this needs to be further evaluated. Key words: heart failure, coenzyme Q₁₀, clinical trial.

Coenzyme Q₁₀ (CoQ₁₀) is an obligatory member of the electron transport chain in the mitochondria.¹ It is a fat-soluble quinone with characteristics common to vitamins.² Normally present in high concentrations in cells with high energy turnover (such as myocardial cells), CoQ₁₀ influences the rate of energy liberation from the electron transport chain by regulation of certain key enzymes. Therefore, CoQ₁₀ plays an important role in the bioenergetics of the cell.²,³ Only a fraction of the total pool of CoQ₁₀ is necessary for an optimal electron flux.⁶ It has been suggested that the remaining pool could serve as a scavenger, protecting the cell from lipid peroxidation caused by free oxygen radicals. Coenzyme Q₁₀ protects the ischemic myocardium⁷ and acts as a membrane stabilizer, as well as an indirect stabilizer of the calcium channels of the membranes.⁸

The myocardial content of CoQ₁₀ is lower in patients with severe heart failure than in those with mild heart failure.⁴ In hopes of avoiding any rate-limiting effects from CoQ₁₀, there has been an interest in supplementing CoQ₁₀ in patients with heart failure. During the last 2–5 years, a few rather small placebo-controlled studies revealed a beneficial effect on clinical symptoms and ejection fraction;⁹–¹¹ however, a recent study with a double-blind crossover design was not able to confirm these findings.¹² In an open, long-term follow-up study of 126 patients treated with CoQ₁₀, ejection fraction improved among 71% of the patients.¹³

This investigation was designed to study the effects of CoQ₁₀ on myocardial function expressed as ejection fraction. Secondary objectives were used to explore changes...
in maximal exercise capacity, quality of life, and the
safety profile of CoQ10.

Materials and Methods

Patients
Seventy-nine patients from seven Scandinavian hospi-
tals were randomized into a double-blind crossover study
of CoQ10 versus placebo. Informed consent was obtained
from each patient. To be entered in the study, a patien~
had to have symptomatic stable chronic congestive heart
failure (optimally treated but not with drugs other than
digitals, diuretics, vasodilators, and/or angiotensin-
converting enzyme [ACE] inhibitors for at least 2
months). Exclusion criteria were acute myocardial
infarction (within 2 months), valvular heart disease suit-
able for open heart surgery, symptom-limiting anginal
chest pain, poorly controlled hypertension, primary pul-
monary disease, and renal dysfunction (serum creatinine
> 200 μmol/L).

The patients were stratified according to etiology of
cardiac disease and treatment with ACE inhibitors. Baseline characteristics are presented in Table 1.

Protocol

The study protocol is outlined in Figure 1. Prior to ran-
domization, all patients underwent a thorough evaluation
consisting of medical history, clinical examination, func-
tional classification according to the New York Heart
Association (NYHA), and laboratory testing, including
CoQ10 in plasma, electrocardiography, chest radiograph,
bicycle ergometry, and determination of the ejection
fraction by nuclear angiography. The patients were
randomly assigned to double-blind therapy with CoQ10
or placebo. Coenzyme Q10 100 mg daily (Pharmacia,
Stock-holm, Sweden), or matching placebo was adminis-
tered in capsule form once daily. Patients were followed
monthly at the outpatient clinic. The evaluation outlined
above and in Figure 1 was repeated after 3 and 6 months.
After 3 months, the patients were switched to the alter-
native treatment. The study protocol was approved by the
ethical review board of the Karolinska Institute.

Procedures

All electrocardiograms were standard 12-lead record-
ings. Heart size was calculated from the chest radiograph
according to Jonsell,14 with a normal limit of < 500
mL/m² body surface area for men and 450 mL/m² for
women.

Symptom-limited maximal exercise tests (Wₛₜₐₜ) were
performed in the sitting position on an electrically braked
bicycle ergometer. The workload was increased by 10 W
each minute. Perceived symptoms (anginal chest pain,
dyspnea) and exertion (leg fatigue) were scaled during
the last 15 seconds of every second workload and always
on the last workload; the 10-point scale was applied, as
described by Borg et al.15

Left ventricular ejection fraction data were acquired at
rest, during a slight volume load induced by raising the
legs, and during supine exercise by means of a gam-
macamera (Maxicamera 400 T, General Electric,
Milwaukee, WI). Evaluation of acquisitions was per-
formed with an automatic evaluation program (NUD/Yale
Nuclear Diagnostics, Stockholm, Sweden) using two ven-
tricular regions of interest and a variable region of inter-
est for background subtraction. Ejection fraction during
exercise was obtained after 6 minutes on a workload cor-
responding to 50% of the Wₛₜₐₜ.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD or Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 10</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>69/10</td>
</tr>
<tr>
<td>Etiology (ischemic/nonischemic*)</td>
<td>33/46</td>
</tr>
<tr>
<td>Symptom duration (years)</td>
<td>4.2 ± 4.0</td>
</tr>
<tr>
<td>NYHA class (I/II/III/IV)</td>
<td>13/60/6</td>
</tr>
<tr>
<td>Medication (%)</td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>75</td>
</tr>
<tr>
<td>Diuretics</td>
<td>96</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>60</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82 ± 16</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>125 ± 21</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80 ± 9</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>22 ± 10</td>
</tr>
<tr>
<td>Legs up</td>
<td>21 ± 10</td>
</tr>
<tr>
<td>Exercise</td>
<td>20 ± 9</td>
</tr>
</tbody>
</table>
| Maximal exercise tolera-
  nce (W)                 | 91 ± 30             |
| Plasma level of CoQ₁₀ (mg/mL) | 1.01±0.48 |

*Idiopathic cardiomyopathy, hypertensive heart disease, valvular
heart disease, and other miscellaneous forms. NYHA, New York
Heart Association; CoQ₁₀, coenzyme Q₁₀; ACE, angiotensin-converting
enzyme.
Quality of life was assessed using two self-administered questionnaires that had previously been well documented in terms of reliability and validity. A disease-specific heart failure questionnaire was employed, which was a slightly modified version of the questionnaire developed for the Cooperative North Scandinavian Enalapril Survival Study trial in severe heart failure. In its current form, the questionnaire has 26 items that, apart from giving an overall score, combine into dimensions depicting symptoms, physical activity restrictions, emotional distress, and life satisfaction. Additionally, the sleep dysfunction scale was used to assess the degree of sleep disturbance. The sleep dysfunction scale uses six graded Likert scales and includes four items. As a check, the change in use of sleeping medication was also recorded. In an overall question, the patient rated whether treatment had resulted in a clear improvement, some improvement, no change, some deterioration, or a clear deterioration. A similar question was used in the study by Sharpe et al.

The plasma levels of total CoQ₁₀ were analyzed with a high-performance liquid chromatographic method, extensively described by Edlund. The coefficient of variation of the method is 2%.

Statistical Methods

All statistical tests were based on data collected at months 3 and 6. There was no washout period between treatment periods. Efficacy data were analyzed using a repeated measure analysis of variance to test for treatment, carryover, and strata effects (SAS Institute, Cary, NC). A P value < .05 was considered significant. The correlation between maximal exercise capacity (watts) and the total score of quality of life was tested by the Pearson correlation coefficient using differences from baseline. A P value < .05 was considered significant.

Results

Sixty-nine patients completed the study according to the protocol. Seven patients died, four during the placebo and three during the CoQ₁₀ periods. Three patients were withdrawn because of acute referral to heart transplantation, unassociated illness, and personal reasons, respectively.

The primary endpoint of the study was the effect of CoQ₁₀ on ejection fraction. These results are presented in Figure 2. In general, there was a slight increase in ejection fraction during the CoQ₁₀ period. The only statistically significant difference was observed during volume load (legs up), when ejection fraction increased from 22.6% ± 12.1% on placebo to 25.0% ± 13% on CoQ₁₀ (P < .05).

Symptom-limited maximal exercise tolerance (Fig. 3) increased by 6%, from 94 ± 31 W (placebo) to 100 ± 34 W (CoQ₁₀).

Fig. 2. Results of ejection fraction measurements at rest, during volume load, and during supine exercise shown as individual data points. Means with standard deviations are superimposed (thick shaded lines).
Fig. 3. Results of symptom-limited maximal exercise capacity and heart rate at the highest comparable workload shown as individual data points. Means with standard deviations are superimposed (thick shaded lines).

Fig. 4. Results of Borg scaling at the highest comparable workloads for dyspnea, leg fatigue, and chest pain shown as individual data points. Means with standard deviations are superimposed (thick shaded lines).
Table 2. Means for Differences With 95% Confidence Intervals Between CoQ10 and Placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (rest) (%)</td>
<td>0.5</td>
<td>-1.0 to 2.0</td>
</tr>
<tr>
<td>EF (legs up) (%)</td>
<td>2.0</td>
<td>0.3 to 3.7</td>
</tr>
<tr>
<td>Exercise (W)</td>
<td>5.6</td>
<td>1.1 to 10.0</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>0.5</td>
<td>-2.7 to 3.6</td>
</tr>
<tr>
<td>Borg scaling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-0.7</td>
<td>-1.2 to 0.2</td>
</tr>
<tr>
<td>Legs</td>
<td>-0.6</td>
<td>-1.2 to 0.0</td>
</tr>
<tr>
<td>Pain</td>
<td>-0.1</td>
<td>-0.6 to 0.3</td>
</tr>
</tbody>
</table>

CoQ10, coenzyme Q10; EF, ejection fraction.

W (CoQ10) (P < .05). Heart rate did not differ during exercise at comparable work loads. The most common reasons to stop exercise were dyspnea and leg fatigue. Coenzyme Q10 caused a statistically significant decrease in the score at the end of exercise for dyspnea and leg fatigue (Fig. 4). Means for differences (with 95% confidence intervals) between CoQ10 and placebo are presented in Table 2.

The total score for the quality of life assessment increased significantly from 107 during the placebo period to 113 during the CoQ10 period (P < .05), indicating a general increase in the “feeling of well being.” More specifically, improved parameters by CoQ10 were those related to life satisfaction and physical activity (Table 3).

Discussion

The most important findings in this study were that adjunctive treatment with 100 mg CoQ10 daily to patients with heart failure caused an increase, however slight, in maximal exercise capacity, improved symptoms related to physical activity, and increased life satisfaction. Left ventricular ejection fraction measured during a slight volume load increased significantly. However, this improvement was not sustained during submaximal exercise or at rest.

Of the seven deaths during the study (4 occurred during the placebo period), two patients died of progressive heart failure, two patients died of myocardial infarction, and three patients died suddenly. Only a few side effects were noted (gastrointestinal disturbances during the placebo and CoQ10 periods; 10 patients each; vertigo in 10 patients during the placebo and in 6 during the CoQ10 periods; and dry skin in 4 patients during the placebo and in 6 during the CoQ10 periods). All side effects were minor and none could specifically be related to the CoQ10 period.

Table 3. Results of the Quality of Life Questionnaire

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (mean ± SD)</th>
<th>CoQ10 (mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>107 ± 23</td>
<td>113 ± 22</td>
<td>.016</td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>33 ± 9</td>
<td>35 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Emotions</td>
<td>34 ± 9</td>
<td>36 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Life satisfaction</td>
<td>20 ± 6</td>
<td>21 ± 5</td>
<td>.014</td>
</tr>
<tr>
<td>Physical activity</td>
<td>20 ± 6</td>
<td>22 ± 6</td>
<td>.048</td>
</tr>
<tr>
<td>Sleeping problem</td>
<td>15 ± 5</td>
<td>18 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Sleeping pills</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Overall question*</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>NS</td>
</tr>
</tbody>
</table>

CoQ10, coenzyme Q10; *Patient’s general well being.
sufficient power to examine effects on myocardial function. It also differs from most studies as regards effects on myocardial function. Except for a small increase during volume load, there was no obvious increase of the ejection fraction. In our placebo-controlled study, this finding was less clear than in previous studies.8,9 Earlier investigations used systolic time intervals to measure myocardial function. Radionuclide measurement of ejection fraction is a more established, direct, and accurate method for the expression of left ventricular systolic function than systolic time intervals. An important difference between our study and most previous investigations is the current lack of significant improvement in subjective symptoms expressed as NYHA classes. However, a significant but small improvement in quality of life was noted in the CoQ10-treated group compared to the placebo-treated group. Differences in baseline plasma values of CoQ10 (indicating a deficiency of the substance) can be another explanation for different results. Langsjoen et al.10 reported on similar baseline levels of CoQ10 (0.77–1.04 μg/mL), while Folker et al.4 found substantially lower levels (0.60–0.77 μg/mL) in NYHA class II–IV patients. A difference in methodology is the most likely explanation; however, differences in dietary intake may also influence the results.

The two important limitations of this study are duration of treatment and dosage. Three months might not be enough time to evaluate the final outcome of CoQ10. In particular, mortality, a major endpoint, could not be studied at all and was not included as an objective in this study. Folker et al. emphasized that CoQ10 in its active form is bound to apoproteins.13 The synthesis of these compounds may span a fairly long time period (weeks to months), which may delay the response to CoQ10. Current data suggest that 3 months should be long enough for most patients to experience the possible benefit of CoQ10.9,10,13 Whether the dose of 100 mg CoQ10 daily is sufficient is unknown. Folker et al.4 explored myocardial concentrations of CoQ10. The level of CoQ10 increased 19–86% in five patients who had been receiving 100 mg of the compound during 2–8 months. In a substudy to this investigation, however, 11 patients did not demonstrate any detectable increase in myocardial CoQ10.31 The reason for this discrepancy remains to be studied.

It may be concluded that CoQ10 in this study had a significant but minor adjuvant effect on exercise capacity and symptoms measured as quality of life. The clinical importance of these findings is not entirely clear. Before recommending CoQ10 as supplementary therapy in heart failure, it is desirable to improve the knowledge of its pharmacodynamic properties (dosage–myocardial uptake–effect) and to compare the effects with those of other adjuvant drugs.

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teleradioentenography (a heart volume index). Acta Radiol 1939;20:325–48


**Appendix**

The Q10 study group comprised the following investigators:

Karolinska Hospital, Stockholm, Sweden: Gunilla Forsell, MD, Claes Hofman-Bang, MD, Hans Åström, MD
Danderyd Hospital, Danderyd, Sweden: Nina Rehnqvist, MD, Claes Held, MD, Lennart Forslund, MD, Inge Björkander, MD
Södersjukhuset, Stockholm, Sweden: Johan Hulting, MD
Huddinge Hospital, Huddinge, Sweden: Karl-Erik Karlberg, MD, Marten Rosenqvist, MD
Nacka Hospital, Nacka, Sweden: Andreas Sjögren, MD, Emno Loogna, MD
Falu Hospital, Falun, Sweden: Helge SaeTre, MD, Greger Ahlberg, MD
Rigshospitalet, Copenhagen, Denmark: Svend-Aage Mortensen, MD
Steering Committee: Karl Swedberg MD, (chairman), Ostra Hospital, Gothenburg, Nina Rehnqvist, MD, Danderyd Hospital, Danderyd, Hans Åström, MD, Karolinska Hospital, Stockholm
Safety Committee: Lars Wallentin, MD, Akademiska Hospital, Uppsala, Sweden
Monitors Pharmacia: Gun Setterberg, Bernt Lund