# The Effect of Coenzyme $Q_{10}$ in Patients with Congestive Heart Failure

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**Background:** Coenzyme $Q_{10}$ is commonly used to treat congestive heart failure on the basis of data from several unblinded, subjective studies. Few randomized, blinded, controlled studies have evaluated objective measures of cardiac performance.

**Objective:** To determine the effect of coenzyme $Q_{10}$ on peak oxygen consumption, exercise duration, and ejection fraction.

**Design:** Randomized, double-blind, controlled trial.

**Setting:** University and Veterans Affairs hospitals.

**Patients:** 55 patients who had congestive heart failure with New York Heart Association class III and IV symptoms, ejection fraction less than 40%, and peak oxygen consumption less than 17.0 mL/kg per minute (or <50% of predicted) during standard therapy were randomly assigned. Forty-six patients completed the study.

**Intervention:** Coenzyme $Q_{10}$, 200 mg/d, or placebo.

**Measurements:** Left ventricular ejection fraction (measured by radionuclide ventriculography) and peak oxygen consumption and exercise duration (measured by a graded exercise evaluation using the Naughton protocol) with continuous metabolic monitoring.

**Results:** Although the mean (±SD) serum concentration of coenzyme $Q_{10}$ increased from $0.95 \pm 0.62$ $\mu$g/mL to $2.2 \pm 1.2$ $\mu$g/mL in patients who received active treatment, ejection fraction, peak oxygen consumption, and exercise duration remained unchanged in both the coenzyme $Q_{10}$ and placebo groups.

**Conclusion:** Coenzyme $Q_{10}$ does not affect ejection fraction, peak oxygen consumption, or exercise duration in patients with congestive heart failure receiving standard medical therapy.

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There are numerous reasons to believe that deficiency of coenzyme $Q_{10}$ (ubiquinone) may exacerbate the poor contractility of myocardial cells in patients with heart failure. Not only does coenzyme $Q_{10}$ play a central role in mitochondrial oxidative phosphorylation (1), but it may also act as an antioxidant scavenger (2). Because the myocardium of patients with congestive heart failure demonstrates oxidative stress (3) and coenzyme $Q_{10}$ prevents lipid peroxidation (4), this substance conceivably could prevent myocardial destruction. Furthermore, the concentration of coenzyme $Q_{10}$ is decreased in myocardial cells of patients with advanced heart failure (5), and the extent of myocardial coenzyme $Q_{10}$ deficiency correlates with the clinical severity of heart failure (5, 6).

It is thus not surprising that nutritional supplementation with coenzyme $Q_{10}$ has been proposed as a treatment for congestive heart failure, that it is extensively advertised, and that it is commonly used by patients with this condition. Many small studies have been published, but most were uncontrolled and unblinded. Approximately 31 Japanese clinical reports describe favorable effects with intravenous or oral coenzyme $Q_{10}$ (7). The studies involved only a small number of patients with heart failure and tended to include patients with cardiac disease of various causes. Nevertheless, in 1974 the Japanese government approved marketing of coenzyme $Q_{10}$ for the treatment of heart failure.

The few U.S. and European studies have had conflicting results. Some controlled studies showed no effect (8, 9), but their limitations make the results inconclusive. Other trials noted improvement (10–13), but concerns about end points, small numbers of patients, and the lack of blinding have limited the acceptance of these studies. With such conflicting data, randomized, controlled, and blinded studies are needed to test the hypothesis that patients with advanced heart failure are deficient in coenzyme $Q_{10}$ and that oral supplementation with coenzyme $Q_{10}$ results in clinical improvement. We therefore evaluated the effects of coenzyme $Q_{10}$ supplementation on left ventricular ejection fraction and exercise tolerance in patients with symptomatic heart failure despite standard medical therapy.

## Methods

We performed a randomized, double-blind, placebo-controlled trial to compare the effects of oral coenzyme $Q_{10}$ (200 mg/d) and placebo. The two primary end points were change in ejection fraction, as assessed by nuclear ventriculography, and change in peak oxygen consumption. The study protocol

was approved by the human volunteers committee of the University of Maryland School of Medicine.

### Inclusion and Exclusion Criteria

Patients with New York Heart Association functional class III or IV disease were eligible for inclusion in this study. All patients had ejection fractions less than 40% (documented by radionuclide ventriculography) and maximal oxygen consumption less than 17.0 mL/kg of body weight per minute or less than 50% of the predicted value. These criteria were used to select symptomatic patients who would have the potential to improve. The mean peak oxygen consumption in our patients was 13.1 mL/kg per minute. In comparison, the peak oxygen consumption criterion for cardiac transplantation is generally considered to be less than 14.0 mL/kg per minute, and the mean peak oxygen consumption in nonexercising normal elderly persons (mean age, 67 years) has been reported to be 19.0 mL/kg per minute (14). Patients were required to have been receiving an unchanged medical regimen for at least 1 month. Patients who had previously taken coenzyme $Q_{10}$ were excluded.

### Baseline Testing

At baseline, three procedures were performed. First, a graded symptom-limited cardiopulmonary exercise test using the Naughton protocol was conducted to assess maximal oxygen consumption. The test was performed by the same operator and was repeated until the maximum oxygen consumption measures on two consecutive test results were within 15% of each other. The final test was considered to be the baseline test with which to assess change during therapy. Second, radionuclide ventriculography was performed by using standard techniques. Third, serum concentration of coenzyme $Q_{10}$ was measured as described elsewhere (15). Three patients did not have concentrations obtained at baseline or follow-up.

### Intervention

Patients were randomly assigned to receive 200 mg of coenzyme $Q_{10}$ per day or placebo. Randomization was performed by using a random-number generator. All patients and study personnel were blinded to study group assignment until all data were final. The dosage was chosen to minimize the chance of inadequate treatment. Previous studies reporting benefit with coenzyme $Q_{10}$ supplementation have generally used daily dosages of 100 or 150 mg (6, 7, 9–13, 16–18).

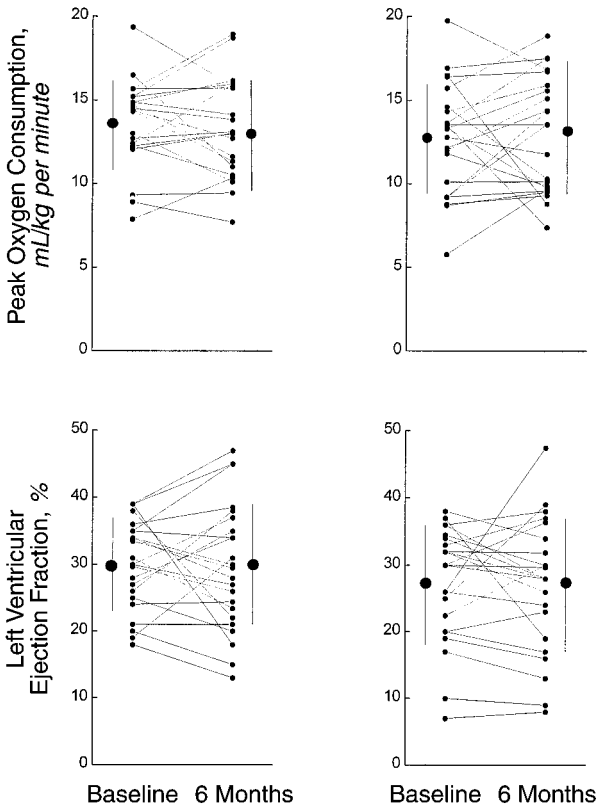


**Figure 1. Ejection fraction and peak oxygen consumption before and after the treatment period for each patient who received placebo (*left*) and coenzyme $Q_{10}$ (*right*).** Coenzyme $Q_{10}$ had no overall effect. The mean ± SD is shown for each time point.

### Final Assessment

After 6 months, all baseline procedures were repeated. At that time, patients were asked whether their symptoms were improved, worse, or the same.

### Statistical Analysis

The change in values of primary and secondary end points were compared by using an unpaired Student *t*-test. All values are given as the mean ± SD. For significance, a *P* value less than 0.05 was required. The study was planned to have 80% power to detect a difference of 2.8 mL/kg per minute in the peak oxygen consumption, with a *P* value of 0.05. This assumed a mean oxygen consumption of 13.0 ± 4.0 mL/kg per minute. We used StatMost, version 3.5 (Dataxiom Software, Inc., Los Angeles, California), for all statistical analyses.

## Results

Fifty-five patients were randomly assigned. Nine patients did not finish the study: 5 in the coenzyme $Q_{10}$ group and 4 in the placebo group. One patient (who was randomly assigned to receive coenzyme $Q_{10}$) was withdrawn from the study before repeated

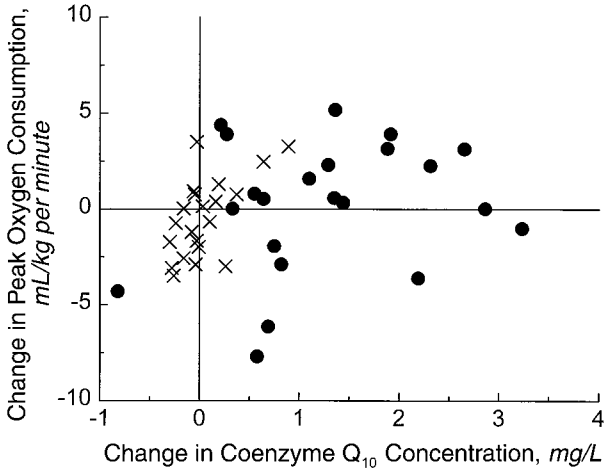


**Figure 2. The change in coenzyme $Q_{10}$ concentration compared with the change in peak oxygen consumption.** Circles represent patients who received active treatment, and crosses represent patients who received placebo. The study drug clearly increased serum concentrations of coenzyme $Q_{10}$. However, there was no relation between the change in serum concentration and the change in peak oxygen consumption.

assessments and unblinding because of error in enrollment criteria. Three patients died: One patient assigned to the placebo group died of progressive heart failure, and 2 patients assigned to the coenzyme $Q_{10}$ group died of myocardial infarction and sudden death, respectively. Four patients did not complete the study because of conditions that prevented them from exercising (esophageal cancer, uncontrolled ventricular tachycardia, foot amputation, and pulmonary edema). One patient randomly assigned to receive coenzyme $Q_{10}$ withdrew from the study.

Baseline characteristics did not differ between the two groups. Twenty-three patients in each group completed the study. The study sample consisted of 39 men and 7 women, and the mean age in both groups was 64 years. Twenty-seven patients had known ischemic heart disease. Forty-two patients were categorized as being in New York Heart Association class III and 4 were in class IV. All patients were receiving digoxin and angiotensin-converting enzyme inhibitors or other vasodilators. Eighteen patients in each group were receiving $\beta$-blockers, and 22 patients in each group were receiving diuretics. No adverse reactions were attributed to the study drug, and no gastrointestinal side effects occurred.

### Maximal Oxygen Consumption

After 6 months of blinded therapy, maximal oxygen consumption did not improve in the placebo or coenzyme $Q_{10}$ group (**Figure 1**). Maximal oxygen consumption increased by $0.21 \pm 3.4$ mL/kg per minute (95% CI, $-1.25$ to 1.68 mL/kg per minute) in the patients who received coenzyme $Q_{10}$ and decreased by $0.49 \pm 2.4$ mL/kg per minute (CI, $-1.54$ to 0.55 mL/kg per minute) in the patients who received placebo. The difference between groups was not significant. The respiratory quotient was $1.01 \pm 0.07$ at baseline and $0.99 \pm 0.07$ after treatment. Exercise duration did not change significantly in either group. In the coenzyme $Q_{10}$ recipients, mean exercise duration was $8.5 \pm 3.2$ minutes before treatment and $9.1 \pm 3.4$ minutes after treatment. In the placebo recipients, exercise duration was $7.7 \pm 3.2$ minutes before treatment and $7.5 \pm 2.9$ minutes after 6 months.

### Radionuclide Ventriculography

Coenzyme $Q_{10}$ had no effect on left ventricular ejection fraction (**Figure 2**). Ejection fraction decreased minimally ($0.3 \pm 8$ percentage points [CI, $-3.7$ to 3.1 percentage points]) in the patients who received coenzyme $Q_{10}$ and decreased by $0.2 \pm 8.6$ percentage points (CI, $-4.0$ to 3.6 percentage points) in the patients who received placebo. Mean left ventricular ejection fraction was 27% before and after treatment in the patients who received coenzyme $Q_{10}$ and was 30% before and after treatment in the patients who received placebo. Right ventricular ejection fraction decreased from $39\% \pm 14\%$ to $37\% \pm 8\%$ in the placebo group. In patients receiving coenzyme $Q_{10}$, right ventricular ejection fraction was $35\% \pm 13\%$ before treatment and $35\% \pm 11\%$ after 6 months.

### Symptoms

One patient in each group had improved symptoms, as indicated by New York Heart Association classification. Almost three quarters of the patients classified themselves as neither improved nor worse after 6 months of treatment (18 patients receiving placebo and 16 patients receiving coenzyme $Q_{10}$). Six patients in the coenzyme $Q_{10}$ group believed that their symptoms had improved even minimally, and one patient believed that symptoms had deteriorated. Two patients in the placebo group reported improvement in symptoms and 3 patients reported increased severity of symptoms.

### Coenzyme $Q_{10}$ Serum Concentrations

Before randomization, coenzyme $Q_{10}$ serum concentrations were similar in both groups. With treatment, concentrations increased in the intervention group from $0.95 \pm 0.62$ $\mu$g/mL to $2.2 \pm 1.2$ $\mu$g/mL; in the placebo group, concentrations did not change ($0.92 \pm 0.34$ $\mu$g/mL before treatment and $0.96 \pm 0.45$ $\mu$g/mL after 6 months). The difference between groups was highly significant ($P < 0.001$). Among patients who received the treatment, serum concentrations increased in 21 of the 22 patients in whom this value was measured (**Figure 2**). Among patients who received placebo, concentrations increased

slightly in only 8 of the 21 patients in whom this value was measured. The increase in patients who received placebo can be explained by small fluctuations in serum concentration or laboratory variability.

No association was seen between change in serum concentration of coenzyme $Q_{10}$ and change in peak exercise oxygen consumption (**Figure 2**) or ejection fraction. This was true for patients in both groups.

## Discussion

In this blinded, randomized, placebo-controlled trial, we detected no objective benefit from coenzyme $Q_{10}$ administration in patients with heart failure. Cardiac performance (measured by ejection fraction) and maximal exercise (evaluated with oxygen consumption and test duration) did not change with coenzyme $Q_{10}$.

The use of coenzyme $Q_{10}$ for the treatment of heart failure has been advocated by both physicians and nonphysicians. Patients use this over-the-counter nutritional supplement extensively, often without the knowledge of their physicians. However, the studies cited to support its use have had major limitations. In addition to open-label studies with obvious susceptibility to unintentional bias (7, 11), some studies have based their conclusions on evaluations of minimally symptomatic and inadequately treated patients (9) or on studies with noncomparable controls, subjective end points, poor statistics, or too few patients (12, 13). The few controlled studies have been contradictory. Our study was blinded and controlled and evaluated moderately and severely ill patients with heart failure who were receiving appropriate standard medical therapy. In addition, the end points were objective and relevant. Our findings suggest that coenzyme $Q_{10}$ should not be recommended for treatment of heart failure.

Evaluations of the effects of coenzyme $Q_{10}$ on ejection fraction have been contradictory. In contrast to our study, one double-blind crossover study of 19 patients with class III and IV heart failure receiving 100 mg of coenzyme $Q_{10}$ per day reported that ejection fraction improved (16). However, the ejection fractions were derived by using echocardiography, not radionuclide ventriculography. In a larger study of 79 patients, resting or exercise ejection fraction did not improve according to radionuclide measurement (10). In that study, a minimal effect on ejection fraction was seen only during volume loading, raising the question of statistical irrelevance. Another blinded crossover trial also did not detect an effect of coenzyme $Q_{10}$ on ejection fraction (9). At present, there is little reason to believe that coenzyme $Q_{10}$ improves ventricular function.

Few studies have evaluated the effect of coenzyme $Q_{10}$ on maximal exercise. These studies present contradictory data; for example, maximal workload was reported to increase slightly in one study (10) but was unchanged in an investigation of minimally impaired patients (9). Our study examined peak oxygen consumption in a randomized, blinded fashion. We found no trend toward an improvement in peak oxygen consumption or exercise duration; thus, it is unlikely that coenzyme $Q_{10}$ improves maximal exercise performance in patients with heart failure.

Many open-label uncontrolled studies have shown a subjective improvement in clinical measures of heart failure (17). Morisco and colleagues' large randomized, blinded trial (18) detected a lower rate of hospitalization for heart failure among patients receiving coenzyme $Q_{10}$. However, this study also reported high rates of pulmonary edema and cardiac asthma in these patients and used vague definitions. The effect on symptoms in other studies have been inconsistent (8, 10). In our trial, most patients reported no change in symptoms.

We studied patients who were receiving standard therapy for heart failure, including $\beta$-blockers for most patients (19). Consequently, our findings should be applicable to the contemporary treatment of heart failure.

In our study, coenzyme $Q_{10}$ supplementation clearly increased serum concentrations in the patients who received active treatment. The increase was dramatic (more than doubling the baseline concentration) and proves that patients took their medication. The lack of correlation between change in coenzyme $Q_{10}$ concentration and change in ejection fraction or peak oxygen consumption supports the conclusion that coenzyme $Q_{10}$ exerted no clinical benefit.

Because of the relatively small size of our study, we cannot definitively say that coenzyme $Q_{10}$ has no effect in patients with heart failure. However, the lack of any trend and the relatively narrow confidence intervals make it unlikely that this nutritional supplement exerts clinically important effects in patients already receiving well-titrated standard medication. The dose given was similar to that given in previous studies that reported positive results. With a documented increase in serum concentrations and a 6-month duration of therapy, the lack of effect cannot be ascribed to inadequate treatment.

In conclusion, our study shows no benefit to adding coenzyme $Q_{10}$ to the standard treatment of heart failure. Chronic illnesses motivate patients to seek out alternative therapy, and it is not surprising that people have been willing to buy an expensive and unproven drug. However, patients should be made aware that coenzyme $Q_{10}$ has been studied in randomized, blinded, and controlled studies and that these studies have found no detectable benefit.

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