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# Response of patients in classes III and IV of cardiomyopathy to therapy in a blind and crossover trial with coenzyme $Q_{10}$

(heart disease/deficiency/bioenergetics)

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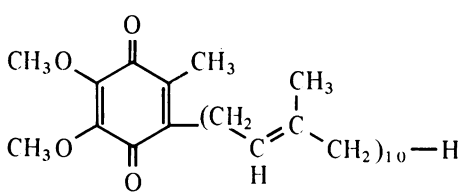
**ABSTRACT** **Coenzyme $Q_{10}$ ($CoQ_{10}$), a biochemically established redox component of respiration including the coupled mechanisms of electron transfer and oxidative phosphorylation, is naturally present in the human myocardium. A double-blind and double-crossover trial has been conducted by administering $CoQ_{10}$ and a matching placebo orally to two groups of patients having class III or IV cardiomyopathy (classification according to criteria of the New York Heart Association). Group A received $CoQ_{10}$ and then placebo; group B received placebo and then $CoQ_{10}$. Blood levels of $CoQ_{10}$ and cardiac function were determined at 0 and 4 weeks (control stabilization period) and at 16 and 28 weeks (after the 12-week CoQ/placebo-treatment periods). For group A, significant increases in $CoQ_{10}$ blood levels and cardiac function occurred during $CoQ_{10}$ treatment and then decreased during crossover to placebo. For group B, there was no change in $CoQ_{10}$ blood levels and cardiac function during placebo treatment, but increases in both parameters occurred in crossover to $CoQ_{10}$. These patients, steadily worsening and expected to die within 2 years under conventional therapy, generally showed an extraordinary clinical improvement, indicating that $CoQ_{10}$ therapy might extend the lives of such patients. This improvement could be due to correction of a myocardial deficiency of $CoQ_{10}$ and to enhanced synthesis of $CoQ_{10}$-requiring enzymes.**

Coenzyme $Q_{10}$ ($CoQ_{10}$) is 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone, **1**, and may be classified with the oil-soluble vitamins, because it is lipoidal. $CoQ_{10}$ is not only present in common diets but is biosynthesized within mammalian tissue.



**1**

Biochemically, $CoQ_{10}$ is a redox coenzyme of the respiratory chain, including the coupled mechanisms of electron transfer and oxidative phosphorylation. These mechanisms, collectively known as "bioenergetics," support life functions. $CoQ_{10}$ is the coenzyme of at least five mitochondrial enzymes: NADH:$CoQ_{10}$ reductase, succinate:$CoQ_{10}$ reductase, electron transfer flavoprotein:$CoQ_{10}$ reductase, reduced $CoQ_{10}$:cytochrome C reductase, and possibly a glycerophosphate:$CoQ_{10}$ reductase. There is also apparently an NADH:$CoQ_{10}$ reductase in the Golgi apparatus.

$CoQ_{10}$ is indispensable in bioenergetics and thus is indispensable to human life itself. The concentration of $CoQ_{10}$ in the human myocardium is high, and it has been presumed for years that a myocardial deficiency of $CoQ_{10}$ would be detrimental to cardiac function. In 1984, the tissue levels of $CoQ_{10}$ in endomyocardial biopsy specimens from 43 patients with cardiomyopathy were reported by Folkers *et al.* (1). Since biopsy samples of healthy hearts were not ethically available, the data on the tissue levels were compared for the four classes of severity of cardiomyopathy. It was found that patients of class IV (most severe) had lower ($P < 0.01$) levels of $CoQ_{10}$ than those of class I (least severe). Patients of combined classes III and IV had a lower ($P < 0.001$) level than those of combined classes I and II. These data demonstrated a myocardial deficiency of $CoQ_{10}$ in cardiomyopathy.

Previously, pure $CoQ_{10}$ had been isolated from human myocardia by Linn *et al.* (2), and a deficiency of a $CoQ_{10}$ enzyme was found in over 100 myocardial biopsy specimens which were taken from cardiac patients at the time of surgery (3–5). In 1980 (6), measurement of the activity of a $CoQ_{10}$ enzyme in blood samples from 1002 cases of cardiac disease showed significantly lower levels ($P < 0.001$) than those in normal subjects.

Patients with heart disease and a left ventricular ejection fraction <30% have a poor prognosis and many such patients are on a progressive downhill course and likely to die within 2 years. Such patients, who were failing to respond to conventional therapy, were found to have decreasing levels of $CoQ_{10}$ in the myocardium with increasing severity of disease (1).

Thus, it seemed that a myocardial deficiency of $CoQ_{10}$ might also be correlated with impairment of cardiac function and performance. This rationale was the basis for the double-blind and double-crossover clinical trial we have conducted, in which capsules of $CoQ_{10}$ and a matching placebo were administered to patients with myocardial disease. The biochemical and clinical results indicate that $CoQ_{10}$ is therapeutically effective in the treatment of cardiomyopathy.

## METHODS

**Biochemistry.** The method for the quantitative determination of $CoQ_{10}$ in human whole blood was that of Vadhanavikit *et al.* (7).

**Patient Selection.** Patients with chronic and moderately advanced but relatively stable myocardial disease were selected. Patients with any ischemic feature, alcoholism, or other life-threatening disease were excluded. All necessary forms of conventional therapy were maintained throughout the study by the primary staff cardiologist. None of the selected patients were in frank congestive heart failure, but all had symptoms of weakness and dyspnea at levels of activity varying from moderate to a sedentary state. The diagnoses were made on the basis of clinical observations, chest x-rays, electrocardiograms, and the echocardiographic find-

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Abbreviation: $CoQ_{10}$, coenzyme $Q_{10}$.

Table 1. Description of patients

| Group | Sex M | Sex F | Age, yr | Heart enlargement None | Heart enlargement Moderate | Pulmonary vascular markings Normal | Pulmonary vascular markings Abnormal | Drug dose: Digitalis Low | Digitalis Med. | Digitalis High | Other antiarrhythmic agents None | Other antiarrhythmic agents Medium | Diuretics Low | Diuretics Med. | Diuretics High | Afterload reducing agents* None | Afterload reducing agents* Low | Afterload reducing agents* Med. | Afterload reducing agents* High | Anticoagulants None | Anticoagulants Standard |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 6 | 2 | 37–77† | 4 | 4 | 5 | 3 | 4 | 3 | 1 | 7 | 1 | 1 | 5 | 2 | 3 | 1 | 2 | 2 | 5 | 3 |
| B | 5 | 6 | 43–75‡ | 4 | 7 | 7 | 4 | 6 | 5 | 0 | 8 | 3 | 2 | 5 | 3 | 5 | 0 | 4 | 2 | 9 | 2 |

*Agents to reduce blood flow resistance.
†Mean 60.6.
‡Mean 64.2.

ings of global myocardial contractile measurements without evidence of valvular disease. Although coronary angiography was not required for entry to the study, nine patients had been so documented. All patients were in classes III and IV of cardiomyopathy, according to the classification criteria established by the New York Heart Association. After approvals by the Institution Review Board and the Research Committee of The Scott and White Memorial Hospital (Temple, TX) and after consent forms were signed, there was a 4-week stabilization period. Then, the patients were randomly assigned by pharmacy personnel of the Clinic in a double-blind and double-crossover protocol so that patients of group A received $CoQ_{10}$ (33.3 mg) orally three times daily for 12 weeks and then a matching placebo three times daily for 12 weeks. The patients of group B received the placebo and then $CoQ_{10}$. The 100-mg daily dosage was the same as that used in prior studies (8) and was independent of body surface area. On weeks 0, 16, and 28, chest x-rays and electrocardiograms were taken. On weeks 0, 4, 16, and 28, data on all of the following criteria were collected: ejection fraction, stroke volume, complete blood count, erythrocyte sedimentation rate, plasma protein and immunoglobulins, $CoQ_{10}$ blood levels, vital signs, weight, and clinical status.

Compliance was checked by interview of the patients and a count of remaining capsules by pharmacy personnel at the end of each treatment period. Compliance was observed to be generally good but not always perfect. All data on stroke volume, ejection fraction, and $CoQ_{10}$ levels were retained independently until each patient had completed the study. The results of the clinical data from the double-blind and double-crossover trial were analyzed by the Section of Biostatistics of the Clinic.

A description of patients is given in Table 1.

## RESULTS

There was no significant medical difference between the two groups during the 4-week stabilization period. Within each group, the following did not differ significantly between the treatment and placebo periods: pulse rate; systolic and diastolic blood pressure; weight; liver size; edema; venous pressure; blood hemoglobin content; leukocyte count; erythrocyte sedimentation rate; and plasma concentrations of $\alpha_1$, $\alpha_2$, $\beta$, and $\gamma$ globulins, immunoglobulins IgG, IgM, and IgA, albumin, and total protein.

**Biochemical Results.** There were 8 patients in group A, who received $CoQ_{10}$ and then placebo, and 11 patients in group B, who received placebo and then $CoQ_{10}$. The trial was blind, including the double crossover.

The $CoQ_{10}$ blood levels for the two groups were determined for each individual for available samples at the beginning (week 0) and at the end of the 4-week stabilization period and at weeks 16 and 28 during the blind trial. The mean values for the eight sets of $CoQ_{10}$ blood levels are in Table 2. There was no statistically significant difference for the two groups between the $CoQ_{10}$ blood levels at the beginning and at the end of the 4-week stabilization period.

For group A, which was treated first with $CoQ_{10}$, the mean blood level was significantly higher ($P < 0.001$) at week 16 than during the stabilization period. After the crossover to placebo (weeks 16–28), the mean blood levels had decreased to values not different from those of the stabilization-period levels.

For the patients in group B, there was no statistically significant change in $CoQ_{10}$ blood levels during the 4-week stabilization period or during the 12-week placebo treatment. After crossover to $CoQ_{10}$, the mean blood level at 28 weeks had increased ($P < 0.001$).

The data for individuals are given in Figs. 1 and 2. The blood levels for group A ranged from about 1.3 to about 3.7 $\mu$g/ml after 12 weeks of receiving $CoQ_{10}$. The range of blood levels for group B, who received $CoQ_{10}$ after placebo, ranged from about 1.0 to about 3.1 $\mu$g/ml after the completion of $CoQ_{10}$ treatment. In the absence of perfect compliance, it appears that an effective clinical response is likely correlated with $CoQ_{10}$ blood levels of about 2 $\mu$g/ml.

The blood levels of $CoQ_{10}$ of the patients in groups A and B during the initial stabilization period show that these patients in classes III and IV of cardiomyopathy have blood levels that range from a deficient state to a normal level. It was reported in another study (1) that patients of combined classes III and IV had lower ($P < 0.05$) levels of $CoQ_{10}$ than those of combined classes I and II. Different tissues of the human body may have different nutrient support of biosyn-

Table 2. $CoQ_{10}$ levels in whole blood of the patients

| | $CoQ_{10}$ level, $\mu$g/ml | | | |
|---|---|---|---|---|
| | Stabilization period | | Blind treatment | |
| | Week 0 | Week 4 | Week 16 | Week 28 |
| Group A ($n$ = 8) | 0.90 ± 0.14 (a) ($n$ = 7) | 1.04 ± 0.31 (b) ($n$ = 8) | 2.46 ± 0.83 (c) ($n$ = 8) | 1.17 ± 0.47 (d) ($n$ = 8) |
| Group B ($n$ = 11) | 0.77 ± 0.26 (e) ($n$ = 9) | 0.92 ± 0.26 (f) ($n$ = 11) | 0.83 ± 0.26 (g) ($n$ = 11) | 1.71 ± 0.58 (h) ($n$ = 11) |

Significance of differences: a or b vs. d and a vs. b, not significant; a or b vs. c, $P < 0.001$; c vs. d, $P < 0.01$; e or f vs. g and e vs. f, not significant; e or f or g vs. h, $P < 0.001$.

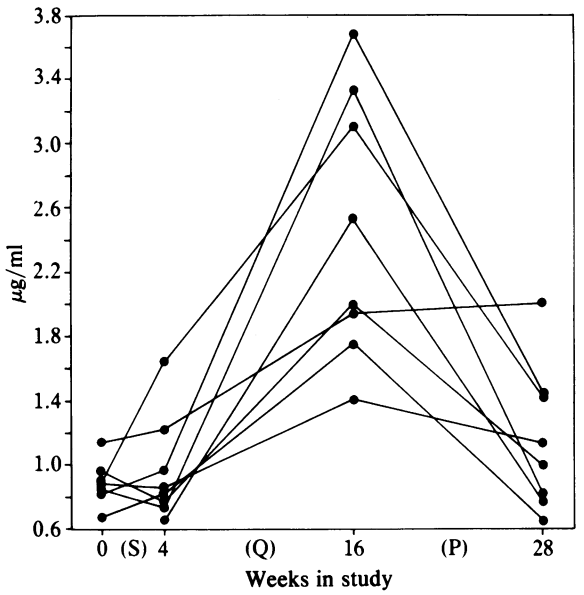


FIG. 1. $CoQ_{10}$ blood levels of patients in group A. The stabilization period (S) and the 12-week periods of CoQ (Q) and placebo (P) administration are indicated. The difference between the mean CoQ concentration at 16 weeks and that at 4 weeks and at 28 weeks is significant ($P < 0.01$).

thesis and metabolic degradation of $CoQ_{10}$. It seems likely that a severe deficiency of $CoQ_{10}$ in the myocardium would be associated with a deficiency in the blood, as observed (1), because of common biosynthetic and metabolic reactions.

**Clinical Results.** Statistical analysis of the measurements of stroke volume, determined by impedance cardiograph (9), reveals a significant difference between the mean base-line value and the mean value after 12 weeks of treatment with $CoQ_{10}$ and a significant difference between the mean value after 12 weeks of treatment and the mean value after the subsequent 12-week period of treatment with placebo (Fig. 3).

The ejection-fraction data were obtained by the method of Weissler *et al.* (10, 11) and were analyzed by using a standard analysis of variance, Student's *t*-test, and linear regression. The normal distributions of each set of ejection fractions were confirmed by the Kolmogorov–Smirnov tests. Contingency tables were evaluated by using $\chi^2$ tests, adjusted for continuity, and Fisher's exact test. Ejection fractions in all patients after $CoQ_{10}$ administration were significantly different ($P < 0.0001$) from mean base-line values and values observed after 12 weeks of placebo administration (Fig. 4). Comparison of $CoQ_{10}$ versus placebo for ejection fractions was significant ($P < 0.0001$), and comparison of corresponding placebo data versus base-line data was not significant. The difference between group A and group B at base-line was not statistically significant. Group A patients, who received first $CoQ_{10}$ and then placebo, still showed a slight increase after placebo as compared with base line; this could be due to residual $CoQ_{10}$, suggesting some carry-over but declining benefit.

In group A, there was indication of worsening myocardial function that paralleled the decreasing blood levels of $CoQ_{10}$

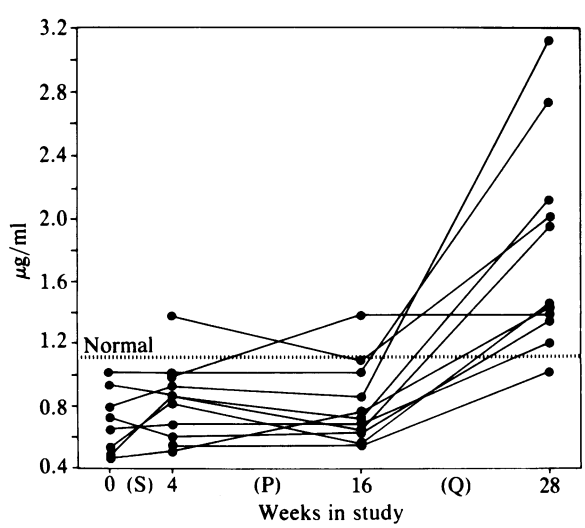


FIG. 2. $CoQ_{10}$ blood levels of patients in group B. Difference between mean value at 16 weeks (before CoQ treatment) and at 28 weeks (after CoQ treatment) is significant ($P < 0.01$).

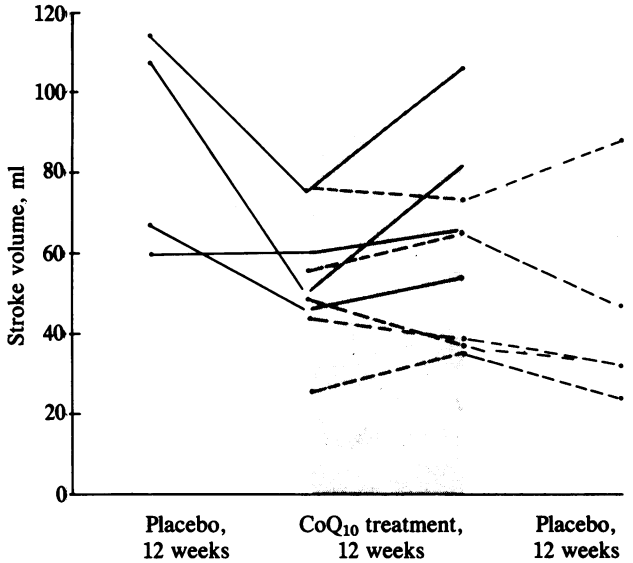


FIG. 3. Data on stroke volume for group A (----) and group B (—).

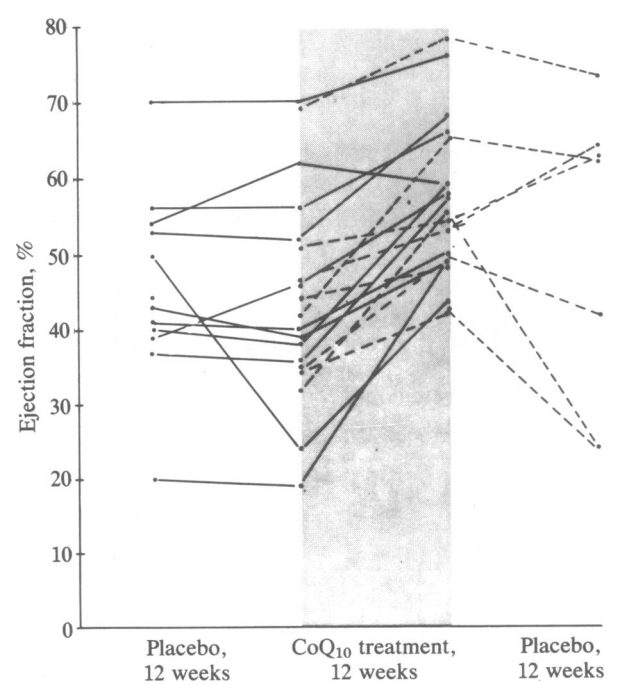


FIG. 4. Data on ejection fraction (%) for group A (----) and group B (—).

during the placebo period, but this change was not statistically significant. Changes in cardiac size, pulmonary vascular markings, and electrocardiogram were observed in 10 of 19 patients. None of the changes were individually significant, but combining these three determinants showed a difference that was significant by Wilcoxon's signed rank test ($P < 0.01$). The change in these combined determinants was toward normality after $CoQ_{10}$ treatment.

Eighteen of 19 patients reported clinical improvement, manifested almost entirely by increases in general activity tolerance. Some of these physical improvements were remarkable. No patient reported any symptom suggestive of intolerance of $CoQ_{10}$.

## DISCUSSION

Some of the patients selected for the study were found to have a blood deficiency of $CoQ_{10}$, as might be expected on the basis of the deficiency of a $CoQ_{10}$ enzyme previously reported for 1002 cardiac patients (6). The finding that not each one of the 19 patients had significant blood deficiencies of $CoQ_{10}$ was appraised in *Results*. Folkers *et al.* (1) reported that biopsies from five patients treated with $CoQ_{10}$ for 2–8 months showed 20–85% increases in myocardial $CoQ_{10}$ levels and the mean value was higher ($P < 0.02$) than before treatment. The data on the effective treatment of cardiomyopathy with $CoQ_{10}$ suggest that a myocardial $CoQ_{10}$ deficiency may be one significant cause of cardiac dysfunction and an indication of etiology. The increases in levels of $CoQ_{10}$ in the blood and in the myocardium after oral treatment show that these deficiencies of $CoQ_{10}$ are treatable. The prompt decline in blood levels in patients receiving placebo after $CoQ_{10}$ (group A) shows that the causes for the initial deficiency were not affected. Generally, and assuming compliance, patients with a lower magnitude of functional increase were those with severe right heart failure with visceral congestion, ascites, hepatomegaly, and high venous pressures. These patients did not, however, uniformly show the lowest base-line blood levels of $CoQ_{10}$.

The best and most accurate measurement of cardiac function was essential to this study, because serial observations were needed to monitor the slow clinical response over weeks of time. Invasive techniques present a difficulty when multiple measurements are needed. Stroke volume and ejection fraction are meaningful criteria. We did find a good correlation of data when the methods of thermodilution and Fick were used simultaneously (unpublished data).

The limited correlation between ejection fraction and the clinical severity of myocardial disease is well known in clinical cardiology, but significant increases in ejection fraction do reflect increases in basic cardiac strength. Radionuclide scans are often used to estimate the ejection fraction, but we chose not to use radionuclide scans as a primary method; the reasons included high cost, inaccuracy in the presence of cardiac arrhythmias, the subjective element of edge analysis which varies with readers, the substantial radiation exposure entailed in four readings over a 7-month period (1200 mR = 24 chest x-rays), and inaccuracy at very low ranges.

The ejection fractions were derived according to Weissler *et al.* (10, 11). This approach to obtaining ejection fractions has proved valuable in our serial monitoring period. Although the numerical values of ejection fraction computed by this method are generally higher than those found in radionuclide studies, it is the relative increases in ejection fraction on a patient-by-patient basis that are important. The ejection fractions reported here were compared with radionuclide measurements by a single scan of each patient at the 28-week checkpoint. The mean value of 58% for ejection fraction by the method of Weissler *et al.* was significantly higher than that of 43% as measured by radionuclide scans. The occasional high ejection fractions recorded were for patients with chronotropic failure, a recognized facet of chronic myocardial disease that permits a functional classification of class III cardiomyopathy.

There was no statistically significant change in vital signs, blood hemoglobin content, leukocyte count, erythrocyte sedimentation rate, or plasma protein and immunoglobulin concentration.

In 1981, Folkers *et al.* (8) reported they had obtained scientific proof of the efficacy of $CoQ_{10}$ in improving cardiac performance based on "super-multiple" monitoring of three prime criteria of the pumping performance of the heart by impedance cardiography. In 1983, Judy *et al.* (12) summarized data showing that $CoQ_{10}$ significantly improved cardiac function in 80% of the patients treated and that the 1-yr survival rate was 71%. Previously, Folkers *et al.* (13) provided a critique of 25 clinical studies in Japan on the treatment of congestive heart failure with $CoQ_{10}$; an encouraging clinical response and an absence of side effects were evident.

We believe that the remarkable clinical improvement of cardiomyopathy patients during $CoQ_{10}$ treatment results from improved bioenergetics which supports improved cardiac function. Empty $CoQ_{10}$-binding sites of apoenzymes may be occupied within a day or two after oral $CoQ_{10}$ administration, thus providing some improvement in cardiac function after 1 week. We believe that the extraordinary improvement in cardiac function that occurs over a longer period may result from slowly increasing levels of $CoQ_{10}$ apoenzymes due to increased synthesis or decreased degradation of these proteins. Although adequate data in support of these concepts are yet to be obtained, one clinically improved patient who was treated with $CoQ_{10}$ after an infarction showed an increased blood level of a $CoQ_{10}$ enzyme after 2 months of treatment (unpublished data). The clinical improvement is most likely due to improved function of impaired but still viable myocardial cells. The reappearance of cardiac dysfunction when $CoQ_{10}$ is replaced with placebo indicates that $CoQ_{10}$ deficiency might be a major if not the sole cause of cardiomyopathy and that $CoQ_{10}$ is likely a lifetime therapy for the cardiac patient.

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