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Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q_{10}

(heart/cardiomyopathy/disease/bioenergetics)

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ABSTRACT **The tissue levels of coenzyme Q_{10} (CoQ_{10}) in endomyocardial biopsy samples and blood from 43 patients with cardiomyopathy were determined by steps of extraction, purification, and HPLC. The biopsy samples were obtained from the patients after a routine heart catheterization. Six patients were of class I, 18 of class II, 11 of class III, and 8 of class IV (classified according to guidelines of the New York Heart Association). True control biopsies of healthy hearts are not available for ethical reasons, but the data of the four classes by severity of disease may be justifiably compared. Patients of class IV had lower ($P < 0.01$) levels of CoQ_{10} than those of class I. Patients of classes III and IV had a lower ($P < 0.001$) level than those of classes I and II. Biopsy samples were obtained from five patients after treatment with CoQ_{10} for 2–8 months. The increases of CoQ_{10} levels ranged from 20% to 85%; the mean value was higher ($P < 0.02$) than before treatment. Blood deficiencies also increase with severity of disease, but not as markedly as for the biopsies. These data reveal a myocardial deficiency of CoQ_{10}, which is higher with increasing severity of disease and is reduced by therapy. This biochemistry correlates with the effective treatment of cardiomyopathy with CoQ_{10}.**

Correlated biochemical rationale, criteria, and data, together with a clinical response, may constitute the best approach to new therapy of disease. The correlation of the biochemical role of coenzyme Q_{10} (CoQ_{10}) in bioenergetics and data on a myocardial deficiency of CoQ_{10}, together with the clinical response of patients with cardiomyopathy to treatment with CoQ_{10}, appear to constitute a major advance for the therapy of cardiomyopathy.

In 1983, at the Fourth International Symposium on the Biomedical and Clinical Aspects of Coenzyme Q (1), there were numerous presentations concerning the therapeutic improvement of the cardiac function of patients having states of cardiac failure. Included were presentations by Judy *et al.*, Hamada *et al.*, Kanazawa *et al.*, Vanfraechem *et al.*, Hiasa *et al.*, Imai *et al.*, Langsjoen *et al.*, Sunamori *et al.*, Tamagawa *et al.*, Hall *et al.*, Folkers *et al.*, Mortensen *et al.*, Wilson *et al.*, and Zilliken *et al.*

Langsjoen *et al.* (ref. 1, pp. 325–332) reported a double-blind crossover trial beginning with 25 patients. These were moderately advanced and reasonably stable cases of chronic myocardial disease of classes III and IV (classified according to the guidelines of the New York Heart Association). Such patients were chosen because they are known to be poorly responsive to conventional forms of therapy and their disease follows a relentless downhill course, generally to death within a year or two. They concluded that CoQ_{10} is a safe and effective therapy for chronic myocardial disease.

Subsequently, Mortensen *et al.* (2) have reported additional data and summarized the long-term CoQ_{10} therapy as a major advance in the management of resistant myocardial failure.

CoQ_{10} may be considered within nutritional science essentially on the basis of its biosynthesis from tyrosine by stepwise enzymic reactions that indispensably require several of the known vitamins in coenzyme form and certain trace elements. Although CoQ_{10} is in most diets, it is also biosynthesized within the mammalian cell. CoQ_{10} is not a vitamin by the 75-year-old definition, but it is vitamin-like on the basis of modern knowledge of the biosynthesis of vitamin C and nicotinic acid.

On the basis of general knowledge of known vitamins in nutrition and medicine, and on the basis of the vitamin-like nature of CoQ_{10}, it may be presumed that CoQ_{10} elicits an intrinsic mammalian response from administration only when a deficiency is present. The possible role of CoQ_{10} as an antioxidant *in vivo* is not necessarily an indispensable biochemical role as is the coenzyme function, but rather one that may nonspecifically take place.

Now that there has been multiple confirmation of the safety and efficacy of CoQ_{10} to treat moderate and advanced cardiomyopathy, it is important to know whether there actually is a myocardial deficiency of CoQ_{10} in patients with cardiomyopathy.

It has been known since 1970 (3–5) that biopsy samples from cardiac surgery (>100 patients) and blood samples (6) from >1000 cardiac patients revealed deficiencies of CoQ_{10}. On the basis of these extensive data, it was anticipated that analysis of endomyocardial biopsies from patients selected for clinical trial with CoQ_{10} would show a significant myocardial deficiency.

We now provide the data and interpretations from the analysis of blood samples and endomyocardial biopsy samples from patients with cardiomyopathy who entered a therapeutic trial with CoQ_{10}. Although there is ethical reluctance to take an endomyocardial biopsy from a responding patient after treatment with CoQ_{10}, data from five such cases may now be included.

METHODS

The techniques of obtaining venous blood samples and endomyocardial biopsy specimens have been described by Mortensen *et al.* (7). The methodology for determining CoQ_{10} in venous blood samples has been described by Vadhanavikit *et al.* (8). The methodology for analysis of biopsy specimens is described by Vadhanavikit *et al.* (9).

RESULTS AND DISCUSSION

The data in Table 1 show the levels of CoQ_{10} that were found in blood samples and in endomyocardial biopsy samples

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

Table 1. Level of CoQ_{10} in blood and biopsy samples of patients with cardiomyopathy

Patient	Diagnosis	Class	Blood CoQ_{10}, μg/ml	Myocardial CoQ_{10}, μg/mg dry wt	
				Left ventricle	Right ventricle
1	Myocarditis	I	0.44	0.30	0.44
2	Myocarditis	I	0.56	0.32	—
3	Dilated cardiomyopathy	I	0.79	0.42	0.40
4	Lung fibrosis	I	1.07	0.48	—
5	Myocarditis/polymyositis	I	0.66	—	0.43
6	Sarcoidosis	I	0.67	—	0.38
		Mean ± SD	0.70 ± 0.22 (a)	0.40 ± 0.06 (b)	
7	Dilated cardiomyopathy	II	1.04	0.28	0.25
8	Dilated cardiomyopathy	II	0.60	0.29	0.41
9	Dilated cardiomyopathy	II	0.75	0.39	0.38
10	Dilated cardiomyopathy	II	0.79	0.38	—
11	Dilated cardiomyopathy	II	1.05	—	0.43
12	Dilated cardiomyopathy	II	0.62	0.30	0.25
13	Dilated cardiomyopathy	II	0.84	0.32	—
14	Dilated cardiomyopathy	II	0.62	—	0.29
15	Dilated cardiomyopathy	II	0.77	0.37	0.39
16	Dilated cardiomyopathy	II	0.57	0.22	—
17	Dilated cardiomyopathy	II	0.63	0.36	0.36
18	Sick sinus syndrome	II	0.80	—	0.26
19	Hypertrophic cardiomyopathy	II	0.89	0.34	—
20	Hypertrophic cardiomyopathy	II	0.47	0.31	—
21	Restrictive cardiomyopathy	II	0.70	0.40	—
22	Small vessel disease	II	1.06	0.41	0.38
23	Small vessel disease	II	0.94	0.37	—
24	Hypertensive heart disease	II	0.77	0.42	—
		Mean ± SD	0.77 ± 0.17 (c)	0.34 ± 0.06 (d)	
25	Dilated cardiomyopathy	III	0.55	0.18	0.32
26	Dilated cardiomyopathy	III	0.64	—	0.29
27	Dilated cardiomyopathy	III	0.73	—	0.30
28	Dilated cardiomyopathy	III	0.53	—	0.28
29	Dilated cardiomyopathy	III	0.48	0.32	0.34
30	Dilated cardiomyopathy	III	0.98	—	0.32
31	Dilated cardiomyopathy	III	0.28	—	0.25
32	Restrictive cardiomyopathy	III	0.40	0.24	0.21
33	Ischemic heart disease	III	0.50	—	0.32
34	Ischemic heart disease	III	0.67	—	0.25
35	Cardiomyopathy/small vessel disease	III	0.84	—	0.29
		Mean ± SD	0.60 ± 0.20 (e)	0.28 ± 0.05 (f)	
36	Dilated cardiomyopathy	IV	0.37	—	0.34
37	Dilated cardiomyopathy	IV	0.95	—	0.26
38	Dilated cardiomyopathy	IV	0.57	0.26	0.27
39	Dilated cardiomyopathy	IV	0.64	—	0.22
40	Myocarditis/polymositis	IV	0.66	—	0.24
41	Ischemic heart disease	IV	0.45	—	0.31
42	Hypertrophic cardiomyopathy	IV	0.74	0.41	—
43	Restrictive cardiomyopathy	IV	0.71	—	0.25
		Mean ± SD	0.64 ± 0.18 (g)	0.28 ± 0.06 (h)	

Blood CoQ level: c vs. e, $P < 0.05$; mean ± SD, a and c = 0.75 ± 0.18 ($n = 24$); mean ± SD, e and g = 0.62 ± 0.19 ($n = 19$); a and c vs. e and g, $P < 0.05$. Myocardial CoQ level: b vs. d, $P < 0.02$; b vs. f, $P < 0.001$; b vs. h, $P < 0.01$; d vs. f, $P < 0.01$; d vs. h, $P < 0.02$; f vs. h, not significant; mean ± SD, b and d = 0.36 ± 0.06 ($n = 33$); mean ± SD, f and h = 0.28 ± 0.05 ($n = 23$); b and d vs. f and h, $P < 0.001$.

from patients with cardiomyopathy. (The data are categorized by the classification of cardiac patients according to the guidelines of the New York Heart Association.)

Since it is not ethically feasible to obtain endomyocardial biopsy samples from normal subjects as controls, 6 patients, most of whom had a myocarditis, but none in failure, were used as a control group. There were 18 patients with class II cardiac disease who suffered no fatigue, palpitation, dyspnea, or anginal pain on ordinary physical activity. There were 11 patients with class III disease who were reasonably comfortable at rest, but suffered the symptoms with minor activity or had a marked limitation of physical activity.

Table 2. Level of CoQ_{10} in blood and biopsy samples of patients after treatment with CoQ_{10}

Patient	Diagnosis	Class	Blood CoQ_{10}, μg/ml		% increase	Myocardial CoQ_{10} right ventricle, μg/mg dry wt		% increase
			Before	After		Before	After	
26	Dilated cardiomyopathy	III	0.64	1.92 (4.5 mo)	200	0.29	0.48 (4.5 mo)	66
27	Dilated cardiomyopathy	III	0.73	1.47 (8 mo)	101	0.30	0.36 (8 mo)	20
32	Restrictive cardiomyopathy	III	0.40	0.73 (8 mo)	82	0.21	0.39 (8 mo)	86
37	Dilated cardiomyopathy	IV	0.95	2.59 (3.5 mo)	173	0.26	0.31 (3.5 mo)	19
38	Dilated cardiomyopathy	IV	0.57	0.80 (2 mo)	40	0.27	0.36 (2 mo)	33
	Mean ± SD		0.66 ± 0.20 (a)	1.50 ± 0.78 (b)		0.27 ± 0.04 (c)	0.38 ± 0.06 (d)	

Patient numbers correspond to the same numbers for patients in classes III and IV for Table 1. a vs. b, not significant; c vs. d, $P < 0.02$.

There were 8 patients of class IV who were unable to perform any physical activity without symptoms, and any physical activity increased their symptoms.

Blood Levels. Interpretation of the blood levels of CoQ_{10} of the four classes of patients indicates that the blood levels can be lower in patients with more severe symptoms (classes III and IV). Although the six subjects of class I, with no overt cardiomyopathy, were used as a control group, these subjects may not have had a true normal level of CoQ_{10}. Since true controls are not available, the best comparisons of data may be between the four classes, because the patients of these groups have increasing degrees of cardiomyopathy. With 18 patients in class II and 11 patients in class III, the mean level of 0.60 ± 0.2 for class III of CoQ_{10} is significantly lower ($P < 0.05$) than the mean value of 0.77 ± 0.17 for class II. It is known that the CoQ_{10} in the leukocyte population is functional, but it is believed that the CoQ_{10} in plasma is presumably nonfunctional and is an equilibrium or balance of absorption and metabolism. Since the major amount of CoQ_{10} in blood is in the plasma, it may be that a significant correlation between plasma and organ levels may exist for the more severe deficiency state, which are indicated by the data in this paper. The independent biosynthesis of CoQ_{10} within myocardial tissue also indicates a possible independence of myocardial and blood levels except, perhaps, for the most severe organ pathology. In spite of these limitations on the blood data, the mean level of blood CoQ_{10} for combined classes I and II was higher ($P < 0.05$) than the mean value for combined classes III and IV.

Biopsy Levels. The data of Table 1 on CoQ_{10} levels in myocardial tissue are quite definitive, in contrast to the limitation of the data on blood levels. The mean CoQ_{10} level of the biopsy samples was 0.40 ± 0.06 for class I as a control, which is significantly higher ($P < 0.02$) than the mean level of 0.34 ± 0.06 for class II. The mean value for class II was significantly higher ($P < 0.01$) than 0.28 ± 0.05 for class III. There was no significant difference between the mean CoQ_{10} levels for the biopsy samples of patients of classes III and IV. By combining the data for classes I and II and for classes III and IV, which increases the values of n for statistical significance, the difference between the means for combined class I and II and combined class III and IV is significant ($P < 0.001$).

These biopsy data on four classes of cardiomyopathy clearly show decreasing tissue levels of CoQ_{10} or increasing levels of deficiency with increasing severity of the symptoms of cardiac disease.

Kitamura *et al.* (ref. 1, pp. 243–252) measured the myocardial tissue level of CoQ_{10} of biopsies from 74 patients who underwent open heart surgery. The specimens weighed between 1 and 5 mg, and the data were calculated on the basis of μg of CoQ_{10} per g of tissue and, presumably, per g wet weight. The data indicated that myocardial levels of CoQ_{10} were lower with increasing severity of heart disease, and that the more severe the heart disease, the higher was the myocardial uptake of the administered CoQ_{10}.

Nobuyoshi *et al.* (ref. 1, pp. 221–229) determined the CoQ_{10} content in serum and myocardial biopsy samples from 72 patients by using a long sheath catheter Olympus bioptome. The data were calculated on the basis of μg of CoQ_{10} per unit amount of protein. The data indicated that the oral administration of 90 mg of CoQ_{10} increased the serum level of CoQ_{10} as well as the myocardial level of the patients.

The data in Table 1 show that the mean myocardial levels of CoQ_{10} numerically differ only slightly with increasing severity of symptoms—i.e., 0.34 ± 0.06 μg/mg, class II; 0.28 ± 0.05 μg/mg, class III; and 0.28 ± 0.06 μg/mg, class IV. The methodology to determine microgram levels of CoQ_{10} in tissue biopsy samples requires as much precision as feasible, and the calculation of CoQ_{10} levels is more precise if based on dry weight of biopsy tissue rather than on variable wet weight or on protein nitrogen. The data in Table 2 show the CoQ_{10} levels in the blood and myocardial biopsies of five of the 43 patients in Table 1. These patients were presumed to take 100 mg of CoQ_{10} daily, but the true degree of compliance is unknown. The blood and myocardial tissues were obtained after periods of therapy ranging from 2 to 8 months. The increases in blood levels of CoQ_{10} ranged from 40% to 200%. It is likely that inadequate compliance or other variables prevented the blood levels of all five subjects from reaching values of 2 μg/ml or higher. The blood levels of two of the five patients are seemingly too low and indicate the poorest compliance.

The data in Table 1 show that the mean CoQ_{10} level of the biopsy samples for class I was 0.40 ± 0.06 μg/mg. Interestingly, the CoQ_{10} biopsy levels of these five patients after treatment ranged from 0.31–0.48 μg/mg, with a mean value of 0.38 ± 0.06 μg/mg (Table 2), which is not significantly different from the mean level for the subjects of class I (Table 1). These increases in myocardial tissue levels range from 20% to 85%, and the actual mean value is higher ($P < 0.02$) than the control level before treatment.

Patient 26 (Table 2) may symbolize a desirable biochemical and clinical result. A low myocardial biopsy level before treatment increased 66% to a presumed normal level, and the blood level increased 200% to 1.9 μg/ml, in 4.5 months. The achievement of blood levels of CoQ_{10} of 2 μg/ml or higher on therapy may well be the desired level, as suggested by Folkers *et al.* (1).

Therapy with CoQ_{10} can result in increasing and even normalizing the myocardial levels of CoQ_{10} under optimum conditions of dosage and compliance. Therapy with CoQ_{10} can result in a profound increase both in cardiac function and in the quality of life of a failing cardiac patient. Cardiomyopathy can be substantially, but not solely, a consequence of a deficiency of CoQ_{10}.

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