Usefulness of Taurine in Chronic Congestive Heart Failure and Its Prospective Application

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We compared the effect of oral administration of taurine (3 g/day) and coenzyme Q_{10} (CoQ_{10}) (30 mg/day) in 17 patients with congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy, whose ejection fraction assessed by echocardiography was less than 50%. The changes in echocardiographic parameters produced by 6 weeks of treatment were evaluated in a double-blind fashion. In the taurine-treated group significant treatment effect was observed on systolic left ventricular function after 6 weeks. Such an effect was not observed in the CoQ_{10}-treated group. (*Jpn Circ J* 1992; **56:** 95–99)

TAURINE (2-aminoethanesulfonic acid) is a nontoxic β-amino acid and a normal constituent of the human diet found in animal food sources, especially fishes and shell fish. It is found in very high concentrations in cardiac tissue, and represents approximately 60% of the free amino acid pool in the mammalian heart. Mammalian cardiac taurine contents vary among the species. Cats are known to be the species most susceptible to taurine deficiency due to poor synthetic capacity. On the other hand, rats have high amount of taurine in the heart, liver and skeletal muscle. Therefore, it may be the natural providence that cats pursue rats.

Although taurine is synthesized by the heart, the major determinant of myocardial taurine is uptake from the plasma. The concentration in myocardium is approximately 100 times that in plasma, indicating active transport process from the plasma. The biochemical aspects of its transport mechanism including changes in taurine content

TABLE IA EFFECTS OF PATHOPHYSIOLOGICAL INTERVENTIONS ON CARDIAC TAURINE CONTENT

Congestive heart failure	↑
Hypoxia	↓
Cardiac necrosis	↓
Ischemia	↓
Cardiomyopathy	↓
Cardiac surgery	↓

TABLE IB ACTIONS OF TAURINE ON THE HEART

1. *Positive inotropy at low calcium concentrations*
2. *Negative inotropy at high calcium concentrations*
3. *Potentiation of digitalis inotropy*
4. *Antagonism of negative inotropy by Ca++ antagonists*
5. *Retardation of lesion development in calcium overload myopathy*
6. *Protection against drug-induced cardiotoxicity*
7. *Protection against calcium paradox- or oxygen paradox-induced myocardial injury*
8. *Antiarrhythmia*
9. *Modulation of cardiac Ca++ current*
10. *Beneficial effect in experimental models of congestive heart failure*

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resulting from modification of uptake into and leakage from myocardial cells by physiological (e.g., β-adrenoceptor stimulation[1]), pharmacological (e.g., guanidinoethyl sulfonate, or β-alanine[2,3]), or pathophysiological (e.g., congestive heart failure[4-6] ischemia[7] or hypoxia[8]) interventions have been quite well documented (Table IA). However, these physiological and pathophysiological roles in the heart remain uncertain.

Recent evidence has led to the view that taurine has some physiological or pharmacological actions. For example, taurine increases myocardial contractility[9,10] possibly by a modulation of calcium movement and availability for excitation-contraction coupling[11,12] The positive inotropic action of taurine is not mediated by an increase in cyclic AMP[10] or an inhibition of the Na^+-K^+ ATPase activity[13] Taurine produces a biphasic contractile response as a function of the extracellular calcium ion concentration; that is, positive inotropy at low calcium and negative inotropy at high calcium[14] Taurine also potentiates the inotropic response to digitalis glycosides[15] and antagonizes the negative inotropic effect of adrenergic β-receptor antagonists and calcium-channel blockers[16] Furthermore, administration of taurine has been shown to prevent a reduction in cardiac function, delay the onset of symptoms associated with cardiac failure, and reduce the mortality rate in animal models of heart failure[6] Recently, cats fed diets deficient in taurine have been reported to have a higher prevalence of dilated cardiomyopathy than cats fed diets high in taurine[17]

Taurine also has protective effects against cardiac injury due to calcium overload such as (a) progression of the lesion in cardiomyopathic hamsters[18] (b) cardiotoxicity induced by isoproterenol and doxorubicin[19,20] and (c) calcium paradox- or oxygen paradox-induced myocardial injury[21,22] Interestingly, a direct negative relation between the severity of myocardial damage caused by calcium paradox and the level of myocardial taurine content has been reported. The cardiovascular actions of taurine are summarized in Table IB.

We have previously reported the clinical utility of taurine for the treatment of congestive heart failure (CHF) using a double-blind crossover trial[23,24] The study demonstrated that taurine had significantly superior efficacy to placebo, as indicated in the final overall improvement, and produced no serious side effects. In an attempt to further clarify the clinical effect of taurine on CHF and to define its clinical position as a therapeutic agent for heart failure, we conducted a double-blind comparative study using coenzyme Q_{10} (CoQ_{10}) as a control agent.

METHODS

Seventeen patients 11 men, 6 women) with chronic CHF and documented left ventricular dysfunction by echocardiography (EF less than 50%) despite successive conventional medical treatment (mean NYHA class 2.5) were entered into the study. The etiology was idiopathic dilated cardiomyopathy in 9 patients and coronary artery disease in 8 patients. The mean EF by echocardiography was 39%. Each patient was randomly allocated to 1 of the 2 treatment groups: daily dose of taurine 3g or CoQ_{10} 30 mg, both of these doses have already been approved for the treatment of congestive heart failure in Japan. The test substances, 1 sachet (taurine 1g or placebo) and 1 tablet (CoQ_{10} 10 mg or placebo), were given orally 3 times a day after meals. All patients were continued with previously prescribed medication (such as digoxin, diuretics, and/or vasodilators) throughout the study period. The total study period was eight weeks, including a 2-week preliminary phase followed by a 6-week double-blind phase. At the end of the study a complete physical examination was performed and resting electrocardiography and M-mode echocardiography were recorded. Volumes were calculated by means of Teichholtz formula.

RESULTS

A total of 17 patients were treated and followed, of these, 10 patients were in the taurine (3 g/day) group and 7 in CoQ (30 mg/day) group. No significant differences in either the severity of the clinical signs and symptoms (data not shown) or in the patients' characteristics were observed among the 2 treatment groups. The general im-

TABLE II HEMODYNAMIC FINDINGS BY ECHOCARDIOGRAPHY

	Group	Baseline Mean (SEM)	After treatment Mean (SEM)
HR (/min)	T	72 (5)	74 (4)
	CoQ	68 (7)	71 (9)
SV (ml)	T	69 (8)	84 (7)*
	CoQ	61 (6)	63 (8)
CO (l/min)	T	4.8 (0.5)	6.3 (0.7)**
	CoQ	4.1 (0.5)	4.1 (0.3)
EF (%)	T	39 (3)	47 (3)**
	CoQ	39 (3)	41 (4)
mVcf (/sec)	T	0.55 (0.04)	0.72 (0.06)**
	CoQ	0.54 (0.04)	0.59 (0.05)

*T=Taurine 3g (n=10); CoQ=CoQ_{10} 30 mg (N=7); HR=Heart rate; SV=Stroke volume; CO=Cardiac output; EF=Ejection fraction; mVcf=Mean velocity of circumferential fiber shortening; *=Significant differences vs. baseline by paired t-test (*$p<0.05$, **$p<0.01$).*

provement assessed by the investigater without knowledge of the treatment group of the patient was 70% in taurine group and 71% in CoQ group. During treatment with taurine or CoQ_{10} for 6 weeks, neither heart rate nor blood pressure changed significantly. There was a significant improvement in systolic left ventricular function with increased cardiac output and stroke volume, EF, and mean Vcf in taurine group, but not in CoQ_{10}-treated group (Table II). Comparison of taurine versus CoQ_{10} for the improvement of these parameters was significant. No adverse effects, including electrocardiographic abnormalities, were observed during the study period.

DISCUSSION

The treatment of CHF has mainly consisted of rest, restriction of dietary sodium and the use of diuretics and cardiac glycosides. Recently, manipulation of cardiac preload and afterload with vasodilating drugs has become a widely accepted therapy. Since CHF is usually caused by ventricular systolic dysfunction, the search for pharmacologic agents capable of augmenting cardiac contractility has been extensively pursued. However, positive inotropic agents do not consistently improve the clinical status of the patients. Inotropic stimulation, by increasing energy expenditure, could contribute to progressive myocardial cell death?[25] Some investigators believe that the long-term administration of positive inotropic agents that act by increasing either intracellular calcium concentration or cyclic AMP levels or both may ultimately be deleterious?[26]

CoQ_{10} exists in the inner membrane of mitochondria and plays a major role in the energy production system (oxidative phosphorylation) as an electron transporter. The myocardial levels of CoQ_{10} in patients with severe CHF were lower than those in patients without symptoms?[27] The remarkable clinical improvemnt of cardiac failure patients during CoQ_{10} treatment, demonstrated by a blind and crossover trial, was ascribed to correction of a myocardial deficiency of this agent?[28] Protective effects of this agent have been demonstrated in animal models of myocardial ischemia, calcium-paradox damage and adriamycin cardiotoxicity?[29] In the present study, symptomatic benefits have been proved in patients treated with CoQ_{10}, but not in terms of M-mode echocardiographic findings.

Taurine is known not to produce adverse side effects, such as increasing heart rate and induction of arrhythmias, that are common to many of the newer inotropic agents presently under research and development. Furthermore, we have reported[6] that taurine delays the onset of symptoms and reduces the mortality rate of heart failure in an animal model. In the same study, the concentration of taurine in the myocardium increased regardless of the quantity of taurine administered. Increased myocardial taurine level was also demonstrated in the heart at autopsy in patients who died from CHF[4] In

dogs with right-sided CHF induced by pulmonary artery ligation, taurine was increased only in the right ventricle, not in the left ventricle or plasma.[30] Thus, in most cases of experimental and clinical heart failure, the myocardial content of taurine is increased and, thus, therapy with taurine might not be expected to be beneficial in this disorder.

In the present study, we have shown the improvement of indexes of cardiac performance in the patients with CHF without adverse effects. Taurine might provide a clue to the elucidation of the mechanisms by which the basic physiological derangement progresses in chronic CHF. It is now apparent that taurine plays a role in the regulation of intracellular calcium homeostasis through modulation of cation fluxes.[12] Taurine enhances calcium availability for contraction and at the same time protects against calcium overload injury. These properties are potentially important for the long-term therapeutic use of taurine in treating patients with chronic CHF.

It is possible that taurine might be more effective in some patients than the other therapeutic agents. Long-term, randomized placebo-controlled clinical trials, in which survival is the principal endpoint, will be started soon.

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