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Therapeutic Effect of Taurine in Congestive Heart Failure: A Double-Blind Crossover Trial*

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Summary: In a double-blind, randomized, crossover, placebo-controlled study, we investigated the effects of adding taurine to the conventional treatment in 14 patients with congestive heart failure for a 4-week period. Compared with placebo, taurine significantly improved the New York Heart Association functional class ($p<0.02$), pulmonary crackles ($p<0.02$), and chest film abnormalities ($p<0.01$). A benefit of taurine over placebo was demonstrated when an overall treatment response for each patient was evaluated on the basis of clinical examination ($p<0.05$). No patient worsened during taurine administration, but four patients did during placebo. Pre-ejection period (corrected for heart rate) decreased from 148 ± 14 ms before taurine treatment to 137 ± 12 ms after taurine ($p<0.001$), and the quotient pre-ejection period/left ventricular ejection time decreased from 47 ± 9 to $42\pm8\%$ ($p<0.001$). Side effects did not occur in the patients during taurine. The results indicate that addition of taurine to conventional therapy is safe and effective for the treatment of patients with congestive heart failure.

Key words: taurine, congestive heart failure, systolic time intervals, double-blind test

Introduction

Taurine (2-aminoethanesulfonic acid), a nontoxic amino acid and a normal constituent of the human diet, has been shown to exert a positive inotropic effect in animals (Baskin and Finney, 1979; Dietrich and Diacono, 1971; Dolara *et al.*, 1978; Sawamura *et al.*, 1983; Schaffer *et al.*, 1973). The mechanism of taurine's inotropic action is unclear; it is reportedly ineffective on sodium- and potassium-activated adenosine triphosphatase (Akera *et al.*, 1976), and at the cellular level of cyclic adenosine monophosphate (Sawamura *et al.*, 1983). Orally administered taurine has been reported to be effective in the treatment of patients with congestive heart failure (CHF) (Azuma *et al.*, 1982, 1983). It was the aim of this controlled, randomized, double-blind, crossover study to test the effects by use of the systolic time intervals, of oral administration of taurine for the treatment of CHF.

Methods

Study Patients

Fourteen patients (9 men and 5 women) with congestive heart failure (CHF) were studied. Eight patients had ischemic heart disease, as documented by previous myocardial infarction or ischemic ST-T changes on electrocardiogram. Six patients had primary regurgitant valve disease (mitral and/or aortic). Table I summarizes clinical data of the patients at entry into the study. All patients

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TABLE I Pretreatment characteristics of patients

Patient	Sex	Age (yrs)	NYHA class	Diagnosis	Score[a]	Rhythm	CTR (%)	Basic medication		
								Digitalis	Diuretics	Vasodilator
Placebo → taurine group										
1	M	84	III	IHD	4	AF	52.2	+	+	−
2	M	72	II	IHD	3	AF	44.3	+	−	+
3	M	71	II	IHD	3	SR	52.3	+	+	−
4	F	75	II	IHD	6	SR	69.1	+	+	+
5	M	73	II	MR	7	AF	70.8	+	+	+
6	F	60	II	ARS+MRS	4	AF	60.5	+	+	−
7	M	65	IV	AR+MR	9	AF	73.3	+	+	−
Taurine → placebo group										
8	M	72	II	IHD	6	SR	50.4	+	−	+
9	M	67	IV	IHD	8	SR	65.9	+	+	+
10	M	63	III	IHD	8	AF	65.2	+	+	−
11	F	46	II	IHD	2	SR	42.3	+	+	+
12	F	68	III	MRS	8	AF	61.2	+	+	−
13	F	56	II	AR+MS	4	AF	58.5	+	−	−
14	M	52	III	AR+MS	5	AF	59.2	+	+	−

[a] Refer to Table II.

Abbreviations: AF = atrial fibrillation; AR=aortic regurgitation; ARS = aortic regurgitation and stenosis; CTR = cardiothoracic ratio; IHD = ischemic heart disease; MR = mitral regurgitation; MS = mitral stenosis; MRS = mitral regurgitation and stenosis; SR = sinus rhythm.

were continued on digitalis with diuretic and/or vasodilator therapy for at least four weeks. They received these drugs at the same dosage throughout the study period. The present investigation was in accordance with the Declaration of Helsinki.

Study Protocol

Each patient entered a lead-in period of at least 2 weeks during which time their symptoms and signs were stable despite successive conventional therapy for CHF. After informed consent was obtained, each patient was evaluated. This included a complete medical history, physical examination, resting electrocardiogram, and chest x-ray, so as to estimate their baseline condition. Thereafter, the patients received the test substance.

A daily dose of 6 g taurine or inactive placebo was given in three divided doses. Taurine or placebo was administered for 4 weeks (crossover A), after which a complete physical examination and interview were performed, and chest x-ray and electrocardiogram were taken. The patient was then "down-titrated" for two weeks and baseline data for the following study period (crossover B) were obtained. Patients then received either taurine or placebo (whichever the patient had not received during crossover A) for 4 weeks, after which they were evaluated as at the end of crossover A. The assessment of subjective and objective effects of taurine and placebo was made at the end of each study period and compared to the baseline status. The comparison of the effects was done without knowledge of the study code after the completion of the whole study.

Scoring the Severity of Heart Failure (Clinicoradiographic Score of Heart Failure Severity)

In order to assess the efficacy of taurine semiquantitatively, the severity of heart failure was expressed by a score system that was based on a combination of clinical and radiographic observations. The details are summarized in Table II.

Left Ventricular Systolic Time Intervals Determination

The systolic time intervals for left ventricular systole were measured from simultaneous recordings of the electrocardiogram, phonocardiogram, and carotid arterial pulse tracing obtained with a multichannel direct recorder at a paper speed of 100 mm/s. Weissler's regression equations were used for correction of the pre-ejection period of the left ventricle (PEP), the left ventricular ejection time (LVET), and the total electromechanical systole (QS_2) for their relation to heart rate (Weissler *et al.*, 1968). The corrected values were called PEPI, LVETI, and QS_2I. When atrial fibrillation was observed, the heart rate calculated from the preceding R-R interval was used. All intervals

TABLE II Criteria for determining heart-failure score[a]

Point value	Dyspnea	Crackles	Right-heart failure	Chest-film abnormality
1	Mild to moderate exertional dyspnea	At base only (unilateral)	Edema, or hepatomegaly (≤1.5 f.b.)	Upper zone flow redistribution
2	Paroxysmal nocturnal or increasing exertional dyspnea	At base only (bilateral)	Edema plus hepatomegaly (≤1.5 f.b.), or hepatomegaly (1.5-3 f.b.)	Interstitial edema
3	Orthopnea or nocturnal cough	More than at base(s)	Hepatomegaly (≥3 f.b.)	Alveolar edema, or interstitial edema with pleural effusion
4	Dyspnea at rest	—	—	—
Maximum points/ category	4	3	3	3

[a] A composite clinical score is sum of the highest number of patients for each criterion. The maximum possible score, corresponding to the worst heart failure, is 13 points. When a partial improvement of clinical status occurred, the score was reduced by subtracting 0.5 points from each point value.
Abbreviations: f.b., finger breadth palpable at midclavicular line.

were calculated from the mean of measurement made on 5 consecutive cardiac cycles for sinus rhythm, and 8 cardiac cycles chosen at random whose preceding R-R interval was over 800 ms for atrial fibrillation (Lewis *et al.*, 1974). Atrial fibrillation produces alteration in the usual relationship of the LVET and PEP to heart rate. Weissler *et al.* concluded (Lewis *et al.*, 1974) that systolic time intervals calculated by averaging all beats, including those following short cycle length, can underestimate potential left ventricular performance and this error can be minimized by measuring only those beats with an R-R > 800 ms. Not until after the measurements were completed was the study code broken.

Data Analysis

Observations made before and after taurine and placebo administration were compared using Student's paired *t*-test for paired data. The Mann-Whitney U test was employed for comparison of effect between taurine and placebo. The Wilcoxon matched-pairs signed ranks test was used for paired data to assess the significance of efficacy comparison. Whenever presented, the results were expressed as mean ± SD, and significance was probability (p) less than 0.05 for all comparative data.

Results

Heart Failure Score

The clinical status of 14 patients during the study is shown in Table III. The clinicoradiographic score of heart failure severity fell from 5.8±2.4 before taurine administration to 3.7±2.0 after taurine ($p<0.001$). However, the score did not significantly decrease during the placebo study period. The difference of the heart failure score of each patient was derived by subtracting the score after treatment from the baseline score; a positive effect was defined as a positive value score, favorable responses were observed in 79% (11/14 patients) during the taurine-treated period and in 21% (3/14 patients) during the placebo-treated period; 4 patients worsened during the placebo period, whereas none did so during the taurine period ($p<0.05$).

Considering each clinical manifestation independently (Table IV), the effect of taurine is superior to placebo in improving the New York Heart Association functional class, pulmonary crackle, and chest film abnormalities.

Systolic Time Intervals

The responses of left ventricular performance to taurine were evaluated based on the results of the systolic time intervals measured by blinded investigators (Table V). Taurine did not significantly affect heart rate or mean arterial pressure, but did shorten the PEPI 11±6 ms ($p<0.001$) and QS_2I 9±14 ms ($p<0.05$). Taurine also improved the quotient PEP/LVET (%) from 47±9 during the control period to 42±8 after taurine administration ($p<0.001$) (Table V).

Figure 1 details the effects of taurine on systolic time intervals for 8 patients with ischemic heart disease. The index for PEP was reduced after four weeks of treatment with taurine from 147±13 to 136±10 ms ($p<0.005$). The changes in the LVETI and QS_2I were not significant. The quotient PEP/LVET improved from 47±8 to 42±7 ($p<0.02$).

TABLE III Effects of taurine and placebo

Patient	Heart-failure score[a]						Relative comparative efficacy[c]
	Placebo			Taurine			
	Baseline	After	Difference[b]	Baseline	After	Difference	
Placebo → taurine group							
1	4	5	−1	7	3	+4	T>P
2	3	3	0	3	0	+3	T>P
3	3	4	−1	4	2	+2	T>P
4	6	4	+2	4.5	4	+0.5	T<P
5	7	7	0	8	3.5	+4.5	T>P
6	4	4	0	3	3	0	T=P
7	9	9	0	10	7.5	+2.5	T>P
Mean ±SD	5.1±2.3	5.1±2.3	0±1.0[h]	5.6±2.7	3.3±2.3[e,g]	+2.4±1.7[h]	(z=1.8921, p<0.10)
Taurine → placebo group							
8	7	4	+3	6	6	0	T<P
9	3.5	3.5	0	8	3.5	+4.5	T>P
10	7.5	7	+0.5	8	5.5	+2.5	T>P
11	3	3	0	2	2	0	T=P
12	6.5	9	−2.5	8	6.5	+1.5	T>P
13	2	2	0	4	2.5	+1.5	T>P
14	3	6	−3	5	3	+2	T>P
Mean ±SD	4.6±2.3	4.9±2.5	−0.3±2.0	5.9±2.3	4.1±1.8[d]	+1.7±1.6	(z=1.4676, not significant)
Total mean ±SD	4.9	5.0	−0.1[i]	5.8	3.7[f,g]	2.0[i]	Taurine>placebo
	2.2	2.2	1.5	2.4	2.0	1.6	(z=2.4384, p<0.05)

[a] Heart-failure score representative of each period (see Table II).
[b] Expressed by the equation; difference=$\text{Score}_{\text{baseline}} - \text{Score}_{\text{after}}$.
[c] Relative comparative efficacy of taurine vs. placebo, expressed as follows: T>P; T is more effective than P, T<P; vice versa, and T=P; no significant difference between T and P; (T denotes taurine and P placebo). Wilcoxon matched-pairs signed-ranks test was employed.
P vs. baseline score ([d]<0.05, [e]<0.01, [f]<0.001), and vs. score after placebo ([g]<0.01).
P between two values ([h]<0.05, [i]<0.01).

TABLE IV Effect of taurine vs. placebo on each clinical manifestation of heart failure

	Improved	Unchanged	Aggravated	U-test[a]
NYHA class				
Taurine	4	10	0	z=2.368
Placebo	0	12	2	p<0.02
Dyspnea				
Taurine	6	8	0	z=1.888
Placebo	3	7	4	p<0.10
Crackles				
Taurine	6	8	0	z=2.548
Placebo	1	10	3	p<0.02
Right-heart failure				
Taurine	6	7	1	z=0.681
Placebo	4	9	1	not significant
Chest film abnormality				
Taurine	6	8	0	z=2.548
Placebo	1	10	3	p<0.02

[a] Mann-Whitney U test was employed to assess the difference between taurine and placebo.

TABLE V Effect of taurine on heart rate, blood pressure, and systolic time intervals

		Placebo		Taurine	
		Baseline	After	Baseline	After
Placebo →	Taurine group (n=7)				
	HR (min^{-1})	74±20	72±15	72±15	73±18
	MAP (mmHg)	89± 7	90± 9	87± 9	87±10
	PEPI (ms)	142±24	142±21	143±16	133±15[c]
	LVETI (ms)	381±21	382±20	381±21	381±16
	QS_2I (ms)	523±33	525±33	524±31	514±23
	PEP/LVET (%)	42± 8	42± 8	44± 8	39± 7[a]
Taurine →	Placebo group (n=7)				
	HR	69±12	73±13	70±12	69±12
	MAP	100±14	105±17	104±12	97±17
	PEPI	147±13	146±12	153±10	141± 8[c]
	LVETI	379±35	374±31	368±25	372±33
	QS_2I	526±37	520±32	520±23	513±27
	PEP/LVET	45± 8	46± 7	50± 8	44± 9[b]
Total (n=14)					
	HR	71±16	72±14	71±13	71±15
	MAP	95±12	98±15	95±14	92±15
	PEPI	145±16	145±14	148±14	137±12[c]
	LVETI	380±29	378±27	374±24	377±25
	QS_2I	525±33	522±31	522±26	513±24[a]
	PEP/LVET	44± 8	44± 8	47± 9	42± 8[c]

Data were obtained before and after 4 weeks of treatment with taurine or placebo.
P vs. baseline ([a]<0.05, [b]<0.01, [c]<0.001).
Abbreviations: HR = heart rate; MAP = mean arterial pressure; PEPI = pre-ejection period index; LVETI = left ventricular ejection time index; QS_2I = electromechanical systole duration index.

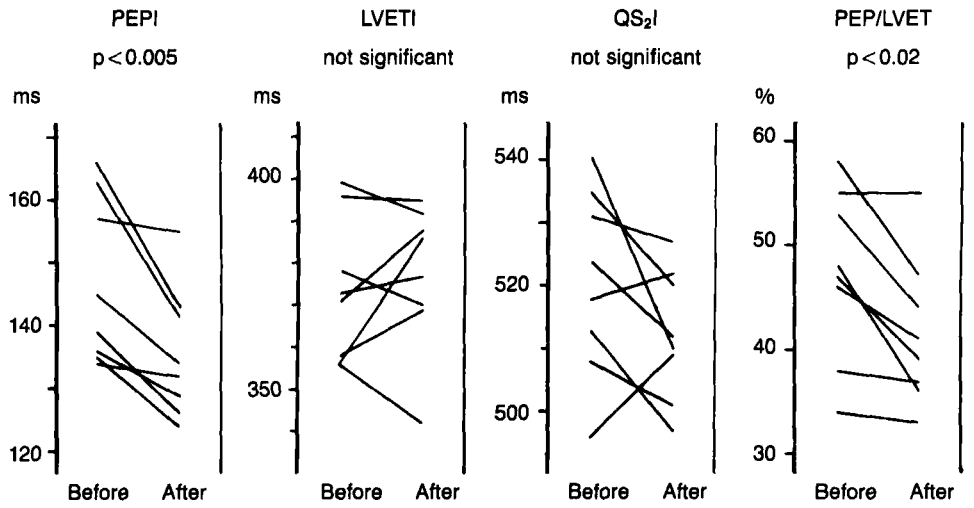

FIG. 1 Effects of taurine on systolic time intervals in patients with ischemic heart disease (n=8). Systolic time intervals obtained before and after 4 weeks of treatment with taurine. LVETI=left ventricular ejection time index; PEPI=pre-ejection period index; QS_2I=electromechanical systole duration index.

Discussion

With an increasing geriatric population, CHF is becoming a very formidable problem. Cardiac glycosides and diuretics remain the keystone in the management of CHF. Despite modern management, however, CHF has proved to be extremely lethal. In the present study oral taurine was added to the conventional therapy for patients with CHF.

The clinical study of CHF is difficult to perform quantitatively without special facilities or techniques due to a lack of consistent diagnostic criteria. Lee and co-workers, using a clinicoradiographic scoring system, compared the effects of oral digoxin with those of placebo (Lee *et al.*, 1982). They documented that such a scoring system for assessing the severity of heart failure is semiquantitative; it is subject to error not only from the inherent arbitrariness of some of the judgements on which it is based, but also from interference by conditions other than heart failure. Even so, they finally concluded that such a scoring system is a reasonable way to estimate the clinical response to digitalis. Populations in the present study differ from those studied by Lee *et al.*; they excluded patients with valvular heart disease and atrial fibrillation. Conditions of over 79% of the patients with prior clinical documentation of heart failure were improved by taurine, as judged by a composite score of clinical and radiographic data. A 21% improvement ratio of clinical manifestations during the placebo period suggests that spontaneous improvement also occurred in the placebo-treated group. Therefore, this would necessitate a double-blind, placebo-controlled trial to obtain proof of the benefit of any agent for treatment of CHF.

Most standard bedside signs of heart failure are qualitative and do not consistently distinguish those with mild from those with severe dysfunction. Systolic time intervals, on the other hand, do provide a quantitative estimate of left ventricular dysfunction. Therefore, measuring systolic time intervals offers a unique noninvasive method in clinical pharmacology for assessing the pharmacological action of cardioactive agents upon the heart (Lewis *et al.*, 1977). When left ventricular failure occurs, regardless of cause, the PEPI lengthens and the LVETI shortens. The PEPI responds in an opposite manner to that of positive and negative inotropic agents. Positive inotropic agents shorten the PEPI, while the LVETI is generally shortened by both positive and negative agents. The QS_2I is also one of the remarkable constants in the circulatory system, and the decrease in QS_2I is a sign of the positive inotropic stimulation (Lewis *et al.*, 1972). The PEP/LVET quotient reflects the overall hemodynamic changes (Garrard *et al.*, 1970; Lewis *et al.*, 1977). This is true independently of the underlying disease (Lewis *et al.*, 1977). Taurine significantly shortened the PEPI, but did not affect the LVETI. Taurine also shortened the QS_2I. There was a significant reduction in PEP/LVET quotient after 4 weeks of taurine administration. These results indicate that taurine is an effective drug for improving the overall hemodynamics in patients with CHF. Taurine affected neither heart rate nor arterial pressure.

In systolic time intervals, improvements of PEPI and PEP/LVET quotient were also obtained in the patients with ischemic heart disease, which were analyzed separately in all patients. This is of importance because the taurine content is decreased in ischemic cardiac muscle produced by coronary artery ligation (Crass and Lombardini, 1977). In these patients, no electrocardiographic evidence of increased myocardial ischemia was observed, and clinical improvement was sustained without aggravation of angina pain. However, whether taurine might augment oxygen consumption, and consequently, result in the exaggeration of the oxygen-deficient condition in ischemic heart disease is not known.

It might be important to appreciate the day-to-day variation of the systolic time intervals even in patients with stable chronic heart disease. Levi *et al.* (1982) demonstrated the spontaneous variation of systolic time intervals between observations and between days. They stressed the necessity of control groups treated with placebo to evaluate the pharmacological effects on the systolic time intervals. We have shown that placebo treatment did not affect any parameters of systolic time intervals, while taurine treatment significantly improved them.

The basic mechanism by which administration of taurine to a group of patients receiving digitalis resulted in substantially improved clinical manifestation and systolic time intervals is not known. The direct positive inotropic action of taurine has previously been demonstrated in a variety of animal heart preparations (Baskin and Finney, 1979; Dietrich and Diacono, 1971; Dolara *et al.*, 1978; Sawamura *et al.*, 1983; Schaffer *et al.*, 1973). Its major inotropic action is not dependent on catecholamine stores or beta-adrenergic receptor sites (Sawamura *et al.*, 1983). *In vitro* study indicates that taurine does not act through inhibition of sodium-postassium ATPase (Akera *et al.*, 1976). Its effect appears to be additive to the inotropic effects of digitalis (Guidotti *et al.*, 1971; Iwata and Fujimoto, 1976). Whether taurine affects excitation–contraction coupling directly or modifies interactions of contractile protein is unknown. All inotropic agents are thought to affect contraction by making more calcium available to the myofilaments. Whether this is the case with taurine, and if so, how it is mediated remains to be elucidated.

Myocardial concentrations of taurine rise in patients who suffer from CHF (Huxtable and Bressler, 1974), and in animal models of cardiac hypertrophy (Peterson *et al.*, 1973). It is not known whether these increases in taurine are causal factors in heart failure, or whether they are secondary to some factors related to the disease process of CHF. Nevertheless, we have shown that oral treatment with taurine improved the status of CHF induced by aortic regurgitation in rabbits (Azuma *et al.*, 1984). Cumulative mortality at 8 weeks in nontreated groups was significantly higher than that in taurine-treated groups.

In summary, the present study shows that taurine is an effective agent for the treatment of heart failure without any adverse effects. Taurine, which is an amino acid and a normal constituent of the human diet, could increase left ventricular performance without any significant changes in arterial pressure or heart rate. However, it should be emphasized that the long-term treatability of CHF with taurine is uncertain. The present observations must therefore be considered preliminary, and long-term study in large populations is necessary. This study should prompt further clinical trials examining the beneficial action of taurine in CHF in more detail.

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