A controlled clinical trial of vitamin E supplementation in patients with congestive heart failure[1–4]

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ABSTRACT

Background: Oxidative stress is increased in patients with congestive heart failure and can contribute to the progressive deterioration observed in these patients. Increased oxidative stress is the result of either an increased production of free radicals or a depletion of endogenous antioxidants, such as vitamin E.

Objective: We aimed to determine whether vitamin E supplementation of patients with advanced heart failure would modify levels of oxidative stress, thereby preventing or delaying the deterioration associated with free radical injury.

Design: Fifty-six outpatients with advanced heart failure (New York Heart Association functional class III or IV) were enrolled in a double-blind randomized controlled trial for 12 wk. At a baseline visit and at 2 follow-up visits, blood and breath samples were collected for the measurement of indexes of heart function and disease state, including malondialdehyde, isoprostanes, and breath pentane and ethane. Quality of life was also assessed at baseline and after 12 wk of treatment.

Results: Vitamin E treatment significantly increased plasma concentrations of α-tocopherol in the treatment group but failed to significantly affect any other marker of oxidative stress or quality of life. In addition, concentrations of atrial naturetic peptide (a humoral marker of ventricular dysfunction), neurohormonal-cytokine markers of prognosis, tumor necrosis factor, epinephrine, and norepinephrine were unchanged with treatment and were not significantly different from those in the control group.

Conclusion: Supplementation with vitamin E did not result in any significant improvements in prognostic or functional indexes of heart failure or in the quality of life of patients with advanced heart failure. *Am J Clin Nutr* 2001;73:219–24.

KEY WORDS Congestive heart failure, vitamin E, tocopherol, supplementation, quality of life, oxidative stress, antioxidants, randomized controlled trial

INTRODUCTION

Oxidative stress is now recognized as an important mechanism for the transduction of several processes recognized to cause apoptosis and cellular injury, irrespective of the initiating factor. Increased free radical activity and oxidative stress were observed in several animal models of cardiac injury, including ischemia-reperfusion injury and catecholamine- and adriamycin-induced heart disease (1–5). In heart failure, both progressive myocyte loss and increased levels of oxidative stress have been observed (6–11).

Increased oxidative stress in heart failure is associated with a relative depletion of endogenous antioxidants, such as vitamin E. Exposure of isolated hearts, cardiac tissue, or intact animals to a free radical–generating system or ischemia followed by reperfusion results in increased oxidative stress and a depletion of the antioxidants superoxide dismutase, glutathione peroxidase, catalase, vitamin E, and glutathione (3, 12–18). Provision of exogenous antioxidants results in reduced peroxidation, improved functional status and better preservation of intracellular structures, and decreased mortality (3, 6, 13, 16, 19–22). Therefore, it has been suggested that an increase in oxidative stress together with a relative deficit of antioxidants is a key factor in the progression of heart failure.

Epidemiologic evidence also supports an inverse relation between vitamin E intake and risk of coronary artery disease (23, 24). However, this epidemiologic evidence was not supported in a recent large, multicenter trial of patients with increased risk of coronary artery disease (25). In addition, although increased oxidative stress has been studied in several models of heart failure, there is currently only one small uncontrolled study of vitamin E supplementation in humans with advanced heart failure (26). Therefore, we conducted a controlled clinical trial to determine whether vitamin E supplementation of patients with advanced heart failure modifies indexes of oxidative and neurohormonal stress and results in an improved quality of life.

SUBJECTS AND METHODS

Patient recruitment

Fifty-six patients were recruited from the outpatient clinics of 12 local cardiologists. Patients were eligible to participate if they

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were judged to have disease of New York Heart Association functional class III or IV, had not taken any multivitamin supplements containing >10 mg (>10 IU) vitamin E/d in the previous 6 mo, could communicate in English, and had adequate liver and kidney function (blood urea nitrogen, creatinine, bilirubin, transaminase, and alkaline phosphatase <2 times normal values). In addition, patients with malignancy or who were clinically unstable were excluded from the study. Forty-six patients had ischemic cardiomyopathy as judged by cardiac catheterization or electrocardiogram or by the appearance of marked segmental dysfunction on echocardiography with an appropriate medical history. In the remaining 10 subjects the source of the cardiomyopathy was unclear. The study was approved by the University of Toronto Committee for Human Experimentation and informed consent was obtained from the subjects before they were randomly assigned to study groups.

The study consisted of 3 visits: a baseline visit and 2 follow-up visits after 6 and 12 wk of supplementation. At each visit, subjects provided a medical history including information on their current medications, their exercise tolerance, and their ability to carry out activities of daily living. Height, weight, and blood pressure were measured at baseline and at each follow-up visit. If an echocardiogram and an electrocardiogram had not been done in the previous 6 mo, then these tests were completed before any treatment was initiated. Blood was collected for baseline measures of electrolytes, liver and kidney function, and indexes of oxidative stress. In addition, expired breath samples were collected for analysis of ethane and pentane. Finally, patients filled out the University of Minnesota Living with Heart Failure questionnaire at baseline and at 12 wk (27). After the collection of baseline data, patients were randomly assigned to receive either vitamin E or placebo. All researchers remained blinded to the nature of the supplements. One capsule from each bottle was retained for analysis. Patients were instructed to take 2 capsules daily (vitamin E or placebo). Pill counts indicated how many of the capsules were consumed and provided an estimate of compliance. Patients were asked to report any adverse effects of the study medication.

Vitamin E and placebo assignment

Patients were randomly assigned with use of a stratified block design by the Toronto Hospital pharmacy. By using a block of 10, each patient number in each cardiac class was assigned the designation of A or B, indicating which supplement the patient would receive. These designations were placed in individual brown envelopes and opened only at the time of randomization. This ensured that all of the study personnel were blinded to the nature of the supplements. Supplements consisted of identical gel capsules that contained either 335.6 mg (500 IU) *RRR*-α tocopherol or placebo (RP Scherer Inc, Windsor, Ontario, Canada).

Blood collection and analysis

At each interview, 25 mL blood was obtained by venipuncture and was centrifuged at 500 × g for 7 min at room temperature in a portable centrifuge (Clinifuge; VWR Canlab, Mississauga Canada). The plasma was separated immediately and portioned for the measurement of indexes of oxidative stress. Plasma was then frozen immediately on dry ice. Blood for measurement of routine biochemistry indexes (electrolytes and kidney and liver function) was delivered to a local laboratory for analysis. The results of this routine analysis were reported to the study coordinator within 48 h. If there were no laboratory values that would exclude the patient from the study, the patient was contacted and instructed to begin taking the supplement.

Measurement of biochemical indexes of oxidative stress

Plasma vitamin E was analyzed by a modification of the method of Bieri et al (28). Malondialdehyde was measured by a procedure adapted from that of Draper (29). The activity of selenium-dependent glutathione peroxidase in plasma was measured by the coupled assay procedure of Paglia and Valentine (30) as modified previously (7). One enzyme unit (activity) was defined as pmol NADPH oxidized to $NADP \cdot min^{-1} \cdot mg\ plasma\ protein^{-1}$. The method used to measure vitamin C (ascorbic acid) determined the total amount of biologically active vitamin C (L-ascorbic acid and dehydro-L-ascorbic acid) colorimetrically (31).

Human tumor necrosis factor and its 2 soluble receptors (RI and RII) were measured by using commercially available kits (Quantikine; R&D Systems, Minneapolis). A high-sensitivity kit was used for the measurement of human tumor necrosis factor (range of detection: 0.5–32 ng/L). All samples were measured in duplicate and all samples from each subject were analyzed in the same run. F_2 isoprostanes were analyzed with an enzyme immunoassay kit (Cayman Chemical Co, Ann Arbor, MI).

Blood for atrial naturetic peptide (ANP) was collected in chilled, EDTA-containing tubes prepared with aprotinin (Sigma, St Louis). ANP was analyzed by using a commercially available enzyme immunoassay kit (Peninsula Laboratories, Belmont, CA). Plasma was separated for the simultaneous measurement of norepinephrine, epinephrine, and dopamine by isocratic ion pair chromatography on a reversed-phase column. The initial sample cleanup with aluminum was performed according to the method of Anton and Sayre (32). Internal standard and sample peak areas were determined by using an HPLC method based on that of Musso et al (33). The inter- and intraassay CVs were <10% and <5%, respectively.

Collection and analysis of breath samples

Subjects were instructed to breathe through a cardboard mouthpiece for 4 min; the mouthpiece was connected to a Tedlar bag through a Rudolph valve (Aerovironment Corp, Munrovia, CA). The bag was filled with hydrocarbon-free air containing <0.01 ppm total hydrocarbons expressed as methane (Air UltraZero; Matheson Gas, Whitby, Canada). The exhaled air was discarded. The initial atmospheric air with its hydrocarbons was flushed from the lungs. During the succeeding 2 min, while the hydrocarbon-free air continued to be inspired, breath was collected into a second bag for pentane measurement. The volume of air collected was recorded by a Wright spirometer attached to the output portion of the Rudolph valve. Throughout the 6 min the nose was closed by a clip. After analysis of the expired breath by gas chromatography, both bags were evacuated and rinsed twice with hydrocarbon-free air before being reused. Bags were filled with hydrocarbon-free air only shortly before use. The analysis of the breath for pentane and ethane was performed as described previously (34).

Statistical analysis

Baseline characteristics, biochemical indexes of oxidative stress, neurohumoral and cytokine markers of prognosis, and comorbid conditions were summarized in terms of frequencies and percentages for categorical variables and by the median and

TABLE 1
Baseline clinical characteristics of the study subjects[1]

Variable	Placebo group (n = 30)	Treatment group (n = 26)
Height (cm)	170	168
Weight (kg)	83	82
BMI (kg/m^2)	28.8	29
Age (y)	64	70
Sex (% male)	77.8	79.2
NYHA class III (%)	88.9	82.6
NYHA class IV (%)	11.1	13
Ejection fraction (%)	23.2 ± 7.9[2]	22.3 ± 9.2
Medications (%)		
ACEI	86.7	69.2
Diuretics	73.3	80.8
Digoxin	73.3	57.7
β-Blockers	10.0	3.9
Amiodarone	20.0	19.2
Aspirin	36.7	30.8
Calcium channel blockers	6.7	23.1
Smoking status (%)		
Never smoked	25.9	29.2
Smoked in the past	66.7	58.3
Present smoker	7.4	12.5

[1] There were no significant differences in any of the variables between groups. NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor.
[2] $\bar{x}$ ± SEM.

25th and 75th percentiles for continuous variables. Comparisons of continuous variables between the placebo and treatment groups were performed with Wilcoxon's rank-sum test. Comparisons of categorical variables between the 2 groups were performed with either the chi-square test or Fisher's exact test. Comparisons of the neurohumoral and cytokine markers of prognosis between the 2 groups were performed by using a repeated-measures analysis of variance model in which the time effect, treatment effect, and the interaction between time and treatment were tested. Analyses were performed with the PROC MIXED procedure in SAS (version 6.12; SAS Institute Inc, Cary, NC).

RESULTS

Clinical characteristics

All patients were in severe heart failure; the mean (±SEM) baseline ejection fraction was 22.5 ± 5.5% and was not significantly different between groups. The clinical characteristics of the patients are presented in **Table 1**. There were no significant differences in sex, weight, body mass index, smoking status, alcohol intake, or intake of other medications between groups. Additionally, the proportion of patients who had stable weights during the study did not differ significantly. The distribution of heart failure classes at baseline and over the 12 wk of the study did not differ significantly between groups. Additionally, there was no significant difference in the distribution of comorbid conditions such as diabetes, hypertension, myocardial infarction, or cardiovascular accidents (**Table 2**).

Biochemical characteristics

Markers of oxidative stress, namely, breath pentane and ethane output and concentrations of malondialdehyde and isoprostanes, were increased compared with normal values for our laboratory (**Table 3**). In contrast, vitamin C, glutathione peroxidase, and β-carotene concentrations were depleted. Baseline vitamin E concentrations were not significantly different from those in healthy control subjects. There were no significant differences between the groups in the markers of oxidative stress and concentrations of antioxidants. Catecholamine and ANP concentrations were above the normal range, but there were no significant differences between groups in concentrations of catecholamines, ANP, and tumor necrosis factor receptor (**Table 4**).

Compliance with treatment

Most patients took >90% of the capsules. However, there was significantly less compliance from 0 to 6 wk than from 6 to 12 wk. Generally, the supplement was well tolerated, with only a few complaints of an oily taste in the mouth that was not significantly different between treatments.

Response to placebo and vitamin E supplementation

In the placebo group, there were no significant changes in breath pentane and ethane output and malondialdehyde and isoprostane concentrations throughout the 12-wk study period (Table 3). Concentrations of vitamin E, vitamin C, and ANP and the catecholamine, norepinephrine, and epinephrine responses also did not change in the placebo group over the 12 wk of study (Table 4).

In the treatment group, vitamin E concentrations doubled between 0 and 6 wk and remained elevated at 12 wk (Table 3). Therefore, vitamin E concentrations were significantly and markedly elevated for ≥6 wk. Vitamin C concentrations did not change significantly in the treatment group throughout the study period. Despite the marked increase in circulating vitamin E, there was no significant reduction in the markers of oxidative stress, including breath pentane and ethane, plasma malondialdehyde, and isoprostanes. In addition, concentrations of ANP, a humoral marker of ventricular dysfunction, and neurohormonal (epinephrine and norepinephrine) and cytokine (tumor necrosis factor) markers of prognosis remained unchanged and were not significantly different from those in the placebo group (Table 4). There was no significant change in the quality of life score in either the placebo group or the treatment group (baseline: 40 and 41; 12 wk: 36 and 35, respectively).

DISCUSSION

Interest in vitamin E has been stimulated by recent epidemiologic studies that showed an inverse relation between vitamin E intake and risk of coronary artery disease (23, 24). Subsequently,

TABLE 2
Comorbid conditions[1]

Condition	Placebo group (n = 30)	Treatment group (n = 26)
	%	
Alcohol consumption	63	45
Cardiovascular accident	7.4	4.2
Diabetes	33.3	41.7
Hypertension	40.7	41.7
History of MI	81.5	66.7

[1] There were no significant differences in any of the variables between groups. MI, myocardial infarction.

TABLE 3
Biochemical indexes of oxidative stress[1]

	Placebo group (n = 30)	Treatment group (n = 26)	Control value[2]
Ethane (pmol·kg^{-1}·min^{-1})			
Baseline	27.2 (17.9, 50.9)[3]	41 (18.4, 72.1)	11.42 ± 0.55
6 wk	28.2 (21.6, 57.3)	26.1 (16.1, 41.6)	—
12 wk	35.2 (23.2, 46.7)	40.6 (22.5, 49)	—
Pentane (pmol·kg^{-1}·min^{-1})			
Baseline	11.3 (4.5, 16.9)	9.8 (4.9, 24.8)	6.06 ± 0.56
6 wk	8.8 (4.5, 15.8)	8.6 (3.0, 13.6)	—
12 wk	5.4 (3.7, 15.2)	7.4 (3.4, 18.5)	—
MDA (μmol/L)			
Baseline	0.46 (0.19, 0.65)	0.61(0.32, 0.84)	0.30 ± 0.04
6 wk	0.38 (0.23, 0.59)	0.52 (0.38, 0.64)	—
12 wk	0.39 (0.25, 0.64)	0.47 (0.26, 0.63)	—
F_2 isoprostanes (nmol/L)			
Baseline	131.2 (96.5, 335.9)	167.3 (43.7, 345.9)	84.33 ± 3.68
6 wk	167.9 (71.6, 377.6)	107.5 (41.1, 189.8)	—
12 wk	96.4 (49.7, 196.8)	100.7 (71.5, 254.4)	—
Vitamin E (μmol/L)[4]			
Baseline	14.3 (12.4, 18.6)	15.1 (10.9, 20.1)	11.3 ± 1.0
6 wk	14.4 (11.1, 18.2)	39.5 (25.2, 56.2)	—
12 wk	14.2 (11.0,19.2)	34.3 (23.7, 54.9)	—
Vitamin C (μmol/L)			
Baseline	40.5 (29.7, 49.5)	39.8 (22.7, 59.7)	71.4 ± 3.8
6 wk	49.0 (38.6, 63.9)	53.0 (45.9, 66.0)	—
12 wk	41.9 (32.4, 61.7)	48.2 (31.3, 66.8)	—
Glutathione peroxidase (AU)			
Baseline	3.2 (2.7, 4.0)	3.6 (2.5, 4.1)	5.4 ± 0.27
6 wk	3.6 (2.7, 4.2)	3.3 (2.1, 4.3)	—
12 wk	3.7 (2.7, 4.4)	3.6 (1.0, 4.3)	—
β-Carotene (μmol/L)			
Baseline	0.3 (0.18, 0.52)	0.24 (0.1, 0.42)	0.40 ± 0.06
6 wk	0.29 (0.15,0.59)	0.23 (0.14, 0.50)	—
12 wk	0.4 (0.25, 0.54)	0.24 (0.14, 0.57)	—

[1] MDA, malondialdehyde; AU, activity units (as defined in Methods).
[2] $\bar{x}$ ± SEM. The range of values found in groups of healthy adults published previously by our laboratory.
[3] Median; 25th and 75th percentiles in parentheses.
[4] Significant treatment × time interaction and significant treatment effect, $P < 0.0001$. No other significant treatment or time effects were identified.

several randomized controlled studies of vitamin E supplementation were carried out in relation to ischemia. In patients with angiographically proven symptomatic coronary atherosclerosis, α-tocopherol treatment substantially reduced the rate of nonfatal myocardial infarction, with beneficial effects apparent after 1 y of treatment (35). There was no benefit for the relative risk of cardiovascular death. In 12 study populations having total plasma cholesterol in the medium range (5.7–6.2 mmol/L) and usual blood pressure, neither of these classic risk factors was significantly correlated with ischemic heart disease mortality, whereas the absolute concentration of vitamin E (α-tocopherol) showed a strong inverse correlation (r^2 = 0.63, P = 0.002) (36). In patients with suspected acute myocardial infarction, a randomized, double-blind, placebo-controlled trial of supplementation with vitamin E plus vitamin A, vitamin C, and β-carotene suggested that these antioxidants may protect against cardiac damage, oxidative stress, and postinfarct complications (37). Results of studies of animal models of heart failure suggest that vitamin E administration may be of considerable benefit (3, 6, 16, 22). However, in contrast with the number of studies related to myocardial ischemia or infarction, only one uncontrolled study was carried out in humans with heart failure. The results of that study suggested that vitamin E reduces oxidative stress (26). The current study is the first randomized controlled trial of vitamin E supplementation in patients with advanced heart failure.

Because the results of our previous study showed that the degree of oxidative stress in heart failure is related to functional class and not to ejection fraction, we selected patients on the basis of New York Heart Association functional class (7) . The patients were evenly matched for clinical characteristics, clinical complications, and drug history. Compliance with supplement taking was very good and the plasma vitamin E concentration attested to the appropriate intake of the capsules.

The plasma catecholamine and ANP concentrations indicated that these patients were in severe heart failure; the raised ethane, pentane, malondialdehyde, and isoprostane concentrations indicated that the patients had significant and severe oxidative stress despite normal vitamin E concentrations. Furthermore, glutathione peroxidase activity was depressed, supporting previous animal studies showing a depletion of antioxidant enzymes during heart failure (3, 6, 8, 16).

Vitamin C is important in recycling the tocopheroxyl (chromanoxyl) radical of vitamin E to an active reduced state (38). Therefore, it is important to have an adequate body content of

TABLE 4
Neurohumoral and cytokine markers of prognosis[1]

	Placebo group	Treatment group
Norepinephrine (nmol/L)		
Baseline	4.4 (3.6, 5.1)	4.7 (3.5, 7.25)
12 wk	4.2 (3.1, 6.0)	4.55 (3.15, 6.15)
Epinephrine (nmol/L)		
Baseline	0.2 (0.1, 0.75)	0.15 (0.1, 0.45)
12 wk	0.2 (0.1, 0.5)	0.1 (0.1, 0.4)
Atrial naturetic peptide (ng/L)		
Baseline	175 (123, 243)	179 (77, 252)
12 wk	156 (104, 296)	195 (126, 241)
Tumor necrosis factor (ng/L plasma)		
Baseline	5.0 (2.1, 7.4)	4.0 (2.4, 7.2)
6 wk	4.9 (2.0, 7.1)	4.5 (3.0, 7.9)
12 wk	5.1 (1.3, 7.2)	4.4 (2.8, 7.5)
sTNF-RI (μg/L)		
Baseline	1.3 (0.97, 1.49)	1.6 (1.1, 2.7)
6 wk	1.4 (0.99, 1.83)	1.8 (1.3, 2.9)
12 wk	1.3 (0.89, 1.55)	1.6 (1.1, 3.0)
sTNF-RII (μg/L)[2]		
Baseline	3.4 (2.8, 4.7)	4.4 (3.3, 6.2)
6 wk	3.4 (2.6, 4.4)	4.6 (3.1, 5.7)
12 wk	3.5 (2.7, 4.1)	4.6 (4.0, 6.1)

[1] Median; 25th and 75th percentiles in parentheses. sTNF-RI and -RII, soluble tumor necrosis factor RI and RII.

[2] Significant treatment effect, $P < 0.0282$. There were no other significant treatment effects, time effects, or time × treatment effects.

vitamin C. Plasma concentrations of vitamin C are a good index of the body content of vitamin C; a plasma concentration >23 μmol/L represents a body content of >600 mg, which is considered to be adequate. However, plasma concentrations are sensitive to recent intake and therefore a single measurement is not as reliable as is a mean of several measurements. The mean vitamin C concentration from 0 to 12 wk in each patient ranged from 25 to 75 and from 29 to 89 μmol/L in the placebo- and vitamin E–treated patients, respectively. These figures suggest that the vitamin C concentration was adequate in these patients and would not have limited the recycling of the tocopheroxyl radical. Furthermore, the concentration of vitamin E doubled and remained elevated in the treatment group. Therefore, our findings suggest that giving as much as 1000 IU *RRR*-α-tocopherol/d alone did not influence indexes of oxidative stress, surrogate markers of ventricular dysfunction, or prognosis and quality of life in these patients with heart failure, despite the fact that plasma vitamin E concentrations were more than doubled.

Our findings are in contrast with those of Ghatak et al (26), who found that supplementation for 4 wk with 400 mg vitamin E effectively reduced concentrations of superoxide ion and improved antioxidant enzyme activity. However, Ghatak et al's study was small (n = 12), was not controlled, and included patients in various stages of cardiac dysfunction. The failure of vitamin E to affect any index of oxidative stress or outcome was also seen in another controlled trial conducted by our group in which a cocktail of antioxidant vitamins, including 1000 IU vitamin E, was provided randomly to patients in the intensive care unit (DJ Hemphill, AA Thomson, CD Mazer, et al, unpublished observations, 2000).

It is possible that the supplementation period of the present study (12 wk) was not long enough to enable clinical changes to be observed; however, antioxidants, if effective, reduce oxidative stress within this period. The fact that vitamin E alone failed to correct the biochemical abnormality for which it was given, despite a substantial increase in plasma concentrations, makes it unlikely that longer treatment would have had a clinical or biochemical effect. In a previous study, we observed a significant decline in breath pentane output in smokers after only 1 wk of vitamin E supplementation, suggesting that our experimental period should have been sufficient to observe changes in lipid peroxidation (39). Furthermore, quality of life scores remained unchanged in the treatment group. Because all subjects had advanced cardiac dysfunction, it is possible that these patients were past the point at which antioxidant supplementation could incur any benefit. This hypothesis can be tested only by conducting further supplementation trials in patients in New York Heart Association functional classes I and II. Finally, it is also possible that supplementation with α-tocopherol alone is insufficient to combat the severe increase in oxidative stress found in patients with advanced heart failure and that the provision of other isoforms of vitamin E, particularly γ-tocopherol, together with a variety of other natural antioxidants may be required for therapeutic efficacy (40). In light of these findings, there is insufficient evidence to support routine supplementation with vitamin E as α-tocopherol alone in patients with advanced heart failure.

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