Vitamin E for coronary bypass operations: a prospective, double-blind, randomized trial

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Vitamin E for coronary bypass operations

A prospective, double-blind, randomized trial

***Background*: Free radical lipid peroxidation contributes to the abnormal metabolism and ventricular function frequently seen after cardiac operations. Antioxidants may improve metabolic and functional recovery. *Methods*: A prospective, randomized, double-blind clinical trial was conducted to determine the effects of vitamin E (alpha-tocopherol) ($n = 14$) or a corn oil placebo ($n = 14$) in patients undergoing elective coronary bypass operations. The RRR-alpha-tocopheryl acetate doubled the alpha-tocopherol levels in the heart. Myocardial metabolism and ventricular function were assessed after the operation. *Results*: Atrial pacing induced myocardial lactate production in the control patients but lactate consumption in the alpha-tocopherol–treated patients on bypass 25 minutes after crossclamp release. Left ventricular stroke work indices were higher, at similar ventricular volumes, in the alpha-tocopherol–treated group, which indicates improved preload recruitable stroke work, and diastolic compliance was greater 4 hours after the operation. The postoperative creatine kinase cardiac isoenzyme levels were lower in the patients who received alpha-tocopherol. *Conclusions*: Pretreatment with alpha-tocopherol sufficient to double the myocardial concentrations had a small but significant metabolic and functional effect after elective coronary bypass operations when compared with placebo. These results do not justify pretreatment of low-risk patients, but they do justify an evaluation in high-risk patients. (J THORAC CARDIOVASC SURG 1994;108:302-10)**

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The mechanism by which reperfusion may exacerbate myocardial ischemic injury has been extensively investigated in recent years. Oxygen-derived free radicals play a significant role in the pathogenesis of reperfusion injury,[1-5] particularly by oxidizing sarcolemmal phospholipids[3-5] and thus disrupting membrane integrity. Vitamin E or alpha-tocopherol is the major and perhaps the only lipid-soluble chain-breaking antioxidant in the myocardial membranes.[6, 7] The most effective form of alpha-tocopherol is the naturally occurring RRR stereoisomer.

We found that phospholipid conjugated dienes, a chemical signature of free radical–mediated lipid peroxidation, were released from the heart[4] and that the antioxidants alpha-tocopherol and glutathione peroxidase[8] decreased after elective coronary bypass operations. We hypothesized that reducing lipid peroxidation by means of exogenous antioxidants might improve intraoperative myocardial protection.

In a preliminary study, we evaluated whether preoperative orally administered RRR stereoisomers of alpha-tocopherol would increase myocardial alpha-tocopherol levels during elective coronary bypass grafting. Then we

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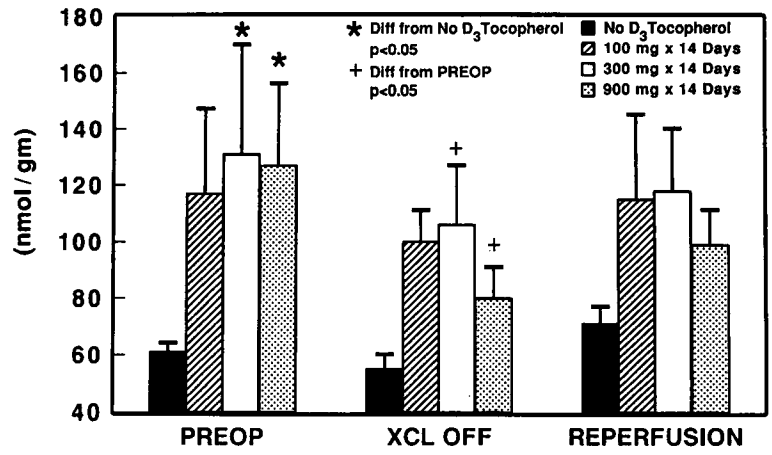

Fig. 1. Total myocardial alpha-tocopherol concentrations (nmol/gm wet weight) before cardioplegia *(PREOP)* were significantly ($p < 0.05$) greater in patients who had received 300 or 900 mg D3-2R,4′R,8′R-alpha-tocopherol *(D_3-tocopherol)* a day for 14 days than in patients in the placebo group. The patients who received 100 mg a day for 14 days had tocopherol levels that were not different from those of the placebo patients ($p > 0.05$). In the patients receiving 300 and 900 mg deuterated alpha-tocopherol, a modest fall ($p < 0.05$) in total alpha-tocopherol levels occurred after crossclamp release *(XCL OFF)*, with recovery after 20 minutes of reperfusion *(REPERFUSION)*.

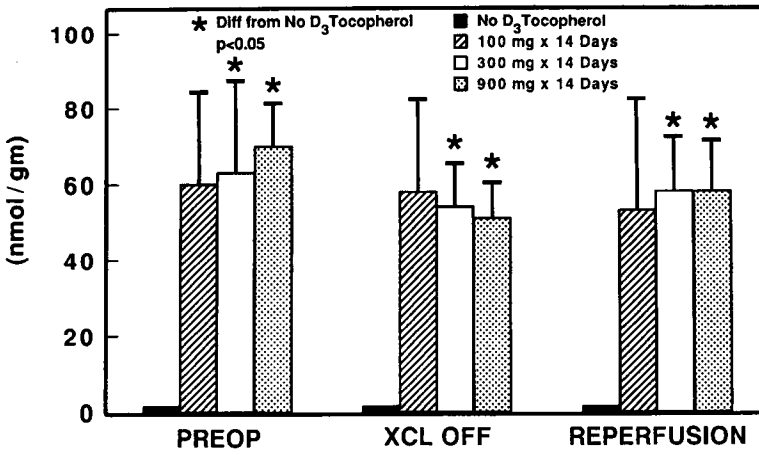

Fig. 2. Myocardial D3-2R,4′R,8′R-alpha-tocopherol *(D_3-tocopherol)* concentrations (nmol/gm wet weight) accounted for the increase in total alpha-tocopherol levels. Deuterated alpha-tocopherol levels were consistently increased in the patients who received 300 or 900 mg a day for 14 days and not in those who received 100 mg per day for 14 days. There were no significant changes in deuterated alpha-tocopherol after crossclamp *(XCL OFF)* and after 20 minutes of reperfusion *(REPERFUSION)*.

performed a prospective, randomized, double-blind trial to determine whether doubling alpha-tocopherol levels would improve postoperative myocardial metabolism and ventricular function.

Methods

Patients. Twenty-six patients agreed to participate in an evaluation of different preoperative doses of alpha-tocopherol on intraoperative left ventricular alpha-tocopherol levels. Twenty-eight patients agreed to participate in a double-blind randomized trial of the effects of 300 mg of alpha-tocopherol given daily for 2 weeks before the operation. All 54 patients signed a consent form approved by the human experimentation committee. The patients were men, aged 42 to 72 years, with stable exertional angina pectoris and preserved left ventricular function (left ventricular ejection fraction greater than 30% on preoperative single-plane contrast ventriculography). Patients receiving vitamin E or any other antioxidant before the operation were excluded.

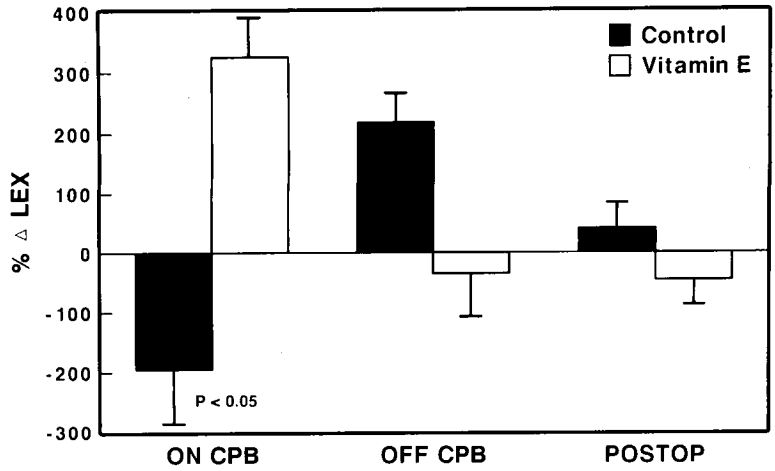

Fig. 3. The change in myocardial lactate extraction *(Δ LEX)* in response to the mild hemodynamic stress of atrial pacing (110 beats/min for 5 minutes) is depicted as a percent change from baseline. Pacing on bypass *(on CPB)* induced lactate release in placebo control patients but an increase in lactate extraction in tocopherol-treated patients ($p < 0.05$). No differences were seen between groups with pacing 25 minutes after discontinuation of bypass *(OFF CPB)* or 4 hours after the operation *(POSTOP)*.

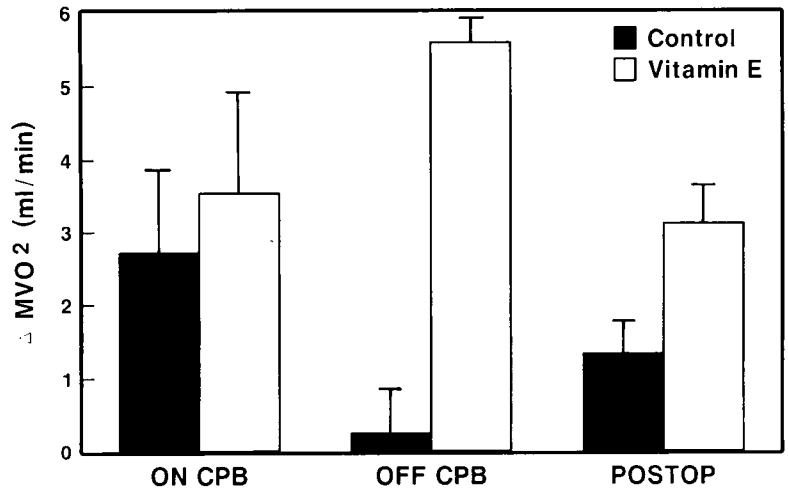

Fig. 4. The increase in myocardial oxygen consumption *(MVO_2)* with atrial pacing (expressed as a change from baseline) was similar for placebo control and vitamin E–treated patients on bypass *(ON CPB)*, 25 minutes after discontinuation of bypass *(OFF CPB)*, and after the operation *(POSTOP)*.

Preparation and administration of alpha-tocopherol. The preparation of deuterium-labeled D3-2R,4′R,8′R-alpha-tocopheryl acetate at the National Research Council of Canada has been described.[9] This compound was supplied in gelatin capsules in a corn oil carrier.

Alpha-tocopherol dose-response study. In a preliminary dose-response study,[10] administering 100, 300, or 900 mg of deuterium-labeled alpha-tocopherol the night before the operation did not raise myocardial alpha-tocopherol levels (D3-alpha-tocopherol 0 ± 0 nmol/gm, alpha-tocopherol 59 ± 3 nmol/gm). A 3-day course of 100 or 900 mg also had no effect.

Patients in the first stage of the study were therefore assigned to one of four groups:

1. No alpha-tocopherol (six patients); corn oil placebo
2. D3-2R,4′R,8′R-alpha-tocopherol acetate given orally as 100 mg daily for 14 days before the operation (six patients)
3. Alpha-tocopherol acetate 300 mg daily for 14 days (eight patients)
4. Alpha-tocopherol acetate 900 mg daily for 14 days (six patients)

Because the 300 and 900 mg dosage schedules were equally

Table I. *Clinical information for prospective randomized trial*

	Placebo	*Alpha-tocopherol*	p *Value*
No.	14	14	
Age (yr)*	59.4 ± 1.8	57.9 ± 1.8	NS
NYHA class (I/II/III/IV)	0/6/7/1	0/6/6/2	NS
LVEF (>60%/40%-60%/20%-40%/<20%)	7/6/1/0	9/4/1/0	NS
No. of diseased vessels (1/2/3)	0/1/13	1/6/7	NS
No. of grafts (1/2/3/4/5)	0/1/2/9/2	1/2/7/4/0	NS
Crossclamp time (min)*	59.3 ± 3.2	56.3 ± 4.4	NS
Bypass time (min)*	118.4 ± 8.0	104.0 ± 6.9	NS

NYHA, New York Heart Association; *LVEF*, left ventricular ejection fraction; *NS*, not significant.
*Mean ± standard error of the mean.

effective in doubling the myocardial alpha-tocopherol concentrations, the prospective trial used 300 mg per day for 14 days. Patients received gelatin capsules containing either the corn oil placebo (14 patients) or the D3-2R, 4′R, 8′R stereoisomer of alpha-tocopherol in the corn oil carrier (14 patients). The capsules were given to the patients after their preoperative visit with their surgeon according to a computer-generated randomized schedule.

Operative technique. Cardiopulmonary bypass was established with a single two-stage right atrial venous cannula and an arterial cannula in the ascending aorta. During bypass, moderate hemodilution (hematocrit value 22% to 24%) and moderate hypothermia (nasopharyngeal temperature of 25° C) were used.

One liter of blood cardioplegic solution (a 2:1 dilution of oxygenated blood/crystalloid solution, delivered through the Buckberg-Shiley Plus System [Shiley Incorporated, Irvine, Calif.]) at 5° C was infused into the aortic root at a root pressure of 70 mm Hg (measured through a separate port of the cardioplegia line [DLP Inc., Grand Rapids, Mich.]). The composition of our blood cardioplegic solution has been described in previous reports.[11]

Proximal and distal anastomoses were constructed during a prolonged crossclamp period. After completion of each distal anastomosis, 100 ml of cardioplegic solution was delivered through the graft. After completion of each proximal anastomosis, 400 ml of cardioplegic solution was infused into the aortic root at a root pressure of 60 mm Hg. The aortic root was vented between cardioplegic infusions.

Normal saline solution at 5° C was used for topical hypothermia. Systemic rewarming was begun during construction of the last distal anastomosis. Left internal mammary grafts were constructed to the left anterior descending coronary artery as the final anastomosis in all patients. A terminal infusion of 500 ml of normothermic cardioplegic solution ("hot shot")[12] was infused into the aortic root before crossclamp removal.

Myocardial biopsies and measurement of alpha-tocopherol levels. In the preliminary dose-response study, full-thickness left ventricular biopsy specimens were obtained with a Tru-Cut needle (William Schmidt, Inc., Valencia, Calif.) during cardiopulmonary bypass at baseline before crossclamp application, immediately after crossclamp release, and after 20 minutes of reperfusion as previously described.[4, 8, 11, 12]

The biopsy specimens were flash-frozen in liquid nitrogen and stored at −80° C for subsequent analysis. 2RS,4′R,8′R-alpha-(5,7,8-[CD_3]$_3$) tocopherol (D9-alpha-tocopherol) was prepared for use as an internal standard.[13] Myocardial biopsy specimens were thawed, excess liquid was removed, and 0.5 ml of water was added, followed by 3.44 nmol of D9-alpha-tocopherol in 25 μl of *n*-decane. Hydrolysis of the sample was carried out by addition of 2 ml of ethanol, containing 1% ascorbic acid and 300 μl of saturated aqueous potassium hydroxide. The vial was incubated at 70° C for 30 minutes and then cooled on ice. *n*-Heptane 4 ml was added and the solution was thoroughly mixed.

Aqueous and organic phases were separated out by brief centrifugation, and 3 ml of *n*-heptane was evaporated with a nitrogen jet. Then 100 μl of pyridine and 50 μl of BSTFA (bis[trimethylsilyl]trifluoroacetamide) silylating reagents were added to the residue. The residue was then heated at 65° C for 15 minutes to convert the tocopherols to their silyl ethers, which have better gas-chromatographic characteristics.

The unlabeled D3- and D9-alpha-tocopherol was analyzed by gas chromatography/mass spectrometry on a Hewlett-Packard 7970A mass selective detector (Hewlett-Packard Company, Andover, Mass.)[13] with single-ion monitoring at 502 d (alpha-tocopherol), 505 d (D3-alpha-tocopherol), and 511 d (D9-alpha-tocopherol). Concentrations of alpha-tocopherol and D3-alpha-tocopherol were calculated with the known quantity of D9-alpha-tocopherol added as an internal standard.

Biochemical measurements. For patients in the randomized trial, a coronary sinus thermodilution flow probe (Webster Laboratories, Baldwin Park, Calif.)[14] and a 5F pediatric feeding tube were inserted into the coronary sinus through the right atrium to allow sampling of coronary sinus effluent and measurement of coronary sinus blood flow.[14]

Arterial and coronary sinus blood samples were assayed for the partial pressures of oxygen and carbon dioxide, pH (Acid-Base Laboratory, Radiometer A/S, Copenhagen, Denmark), and oxygen saturation (Co-Oximeter, Instrumentation Laboratory Inc., Lexington, Mass.).

Lactate concentrations in arterial and coronary sinus blood was determined by mixing the blood with a measured volume of 6% perchloric acid. Lactate concentrations were measured in the protein-free supernatant (Rapid Lactate Stat Pack Kit, Calbiochem-Behring, La Jolla, Calif.). Myocardial oxygen consumption and lactate consumption were then calculated as coronary sinus blood flow multiplied by the difference in arterial and coronary sinus oxygen or lactate concentrations.[11, 12]

The MB isoenzyme of creatine kinase (CK-MB) was measured by an antibody inhibition technique (CK-MB, Boehringer Mannheim, Montreal) five times during the first 24 hours after the operation.

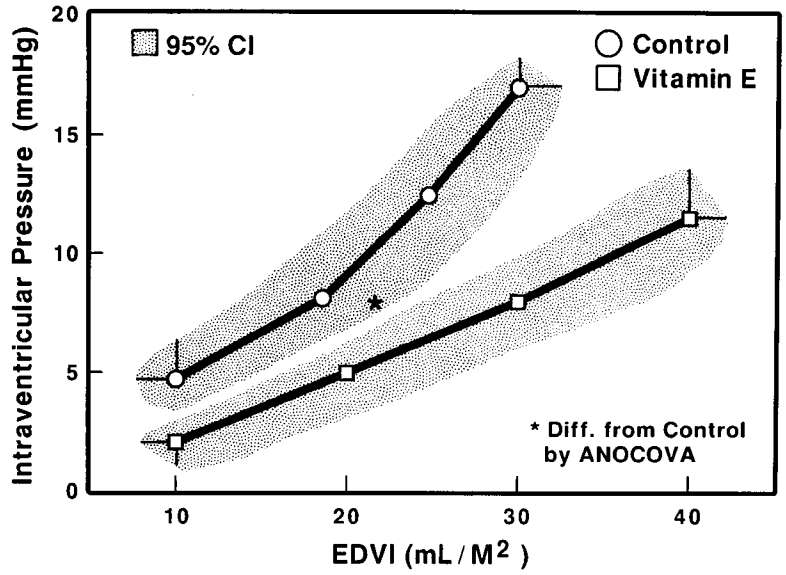

Fig. 5. Diastolic compliance (the relation between the diastolic intraventricular pressures and the diastolic volume indices, *EDVI*) was different ($p < 0.05$) by an analysis of covariance *(ANOCOVA)*. The placebo control patients had higher pressures at lower volumes than the alpha-tocopherol–treated patients. *CI*, Confidence interval.

Timing of measurements. Metabolic measurements were taken during cardiopulmonary bypass before crossclamp application, with each cardioplegic infusion, at crossclamp removal, and then after 10 and 20 minutes of reperfusion during bypass. Measurements were repeated 10 and 20 minutes after bypass was discontinued.

Twenty-five minutes after crossclamp removal, while still supported by bypass, each patient's heart was atrially paced at 110 beats/min for 5 minutes to stress the heart and reveal any latent metabolic dysfunction. Pacing was repeated 25 minutes after discontinuation of bypass. Measurements were taken before and after 5 minutes of pacing.

Four hours after crossclamp removal, hemodynamic and metabolic measurements were obtained at baseline, after volume loading to raise the pulmonary capillary wedge pressure by 4 mm Hg, after a period of equilibration to allow the effects of volume loading to dissipate, and finally after a third period of atrial pacing for 5 minutes at 110 beats/min.

Ventricular function. Four hours after the operation, after patients had been transferred to the intensive care unit and rewarmed, volume repleted, and sedated with intravenous diazepam (0.07 mg/kg) and morphine sulfate (0.06 mg/kg), left ventricular function was evaluated. Ventricular function was assessed at baseline, after volume loading with a sufficient amount of 5% albumin to raise the left ventricular end-diastolic pressure by 4 mm Hg, and after a period of reequilibration to allow the effects of volume loading to dissipate.

Left ventricular volumes were acquired by means of a scintigraphic count-based, nongeometric technique of equilibrium-gated nuclear ventriculography as described by Burns and colleagues.[15] Red blood cells were labeled in vivo with 2.5 mg stannous pyrophosphate, followed 30 minutes later by 25 μCi of technetium 99m pertechnetate. A Technicare Sigma 420 gamma camera with a general-purpose parallel-hole collimator (Technicare Corporation, Solon, Ohio) was placed in a 45-degree left anterior oblique position with 10-degree caudal tilt and adjusted to maximize right and left ventricular separation. A Medical Data System A2 computer (Medical Data Systems, Ann Arbor, Mich.) was interfaced with the gamma camera.

Scintigraphic data were acquired over 2-minute periods at a rate of 32 frames per RR interval. A blood sample was obtained at the midpoint of each study for scintigraphic analysis of technetium 99m–labeled red blood cell counts. The right and left ventricular regions of interest and the background correction were identified with methods similar to those proposed by Maddahi, Berman, and Matsuoka.[16] Scintigraphic counts from the left ventricular region were corrected for background, radioactive decay, dilution, and attenuation. Attenuation was corrected by the following formula:

$$\text{Ventricular volume} = (\text{Corrected ventricular counts} \times e^{-\mu d})/\text{counts/ml blood sample}$$

where e is the natural logarithm, d is the distance from the body surface to the center of the ventricle (determined by triangulation), and μ is the average linear attenuation coefficient (0.16/cm in our laboratory).[15] The reproducibility of volume measurements was within 5% for volume indices between 20 and 70 ml/m^2. The count-based ventricular volume calculations have correlated well with contrast ventriculographic volumes. Left ventricular volumes were calculated for each of the 32 points of the cardiac cycle by our nongeometric count-based method.[15]

Left ventricular pressures were measured by means of a micromanometer (Millar Instruments, Inc., Austin, Tex.) placed into the left ventricle during the operation from the right superior pulmonary vein, and data were collected on a dedicated computer. The pressure measurements collected during acquisition of nuclear ventriculographic data were averaged, and 32 pressure measurements were generated for each RR

interval. A square wave indicating the time at which the gamma camera detected the R wave was output to the computer recording the pressure measurements to synchronize the radionuclide volumes and left ventricular pressure measurements.

Pressure and volume data were synchronized to end-diastole, and pressure-volume loops were constructed from the 32 simultaneous coordinates throughout the cardiac cycle.[17] Each patient had three pressure-volume loops constructed: baseline 1, volume loading, and baseline 2. The pressure-volume loops were generally rectangular, allowing use of the time-varying elastance model for analysis of systolic function.[17-19]

End-systolic elastance was evaluated as the relation between end-systolic pressure and volume indices. Preload recruitable stroke work was assessed by comparing the area within the pressure-volume loop (stroke work index) and the end-diastolic volume index. For the assessment of diastolic compliance, diastolic pressure measurements were first transformed to a natural logarithmic pressure scale, because the diastolic pressure-volume relation was believed to be monoexponential, and then subjected to analysis of covariance for group effects. However, the relation between the untransformed diastolic pressures and the diastolic volume indices was used to display the data. We have previously validated our technique of assessing ventricular function.[18]

Statistical analysis. The SAS programs (SAS Institute, Cary, N.C.) were used for data analysis. Alpha-tocopherol levels and hemodynamic and metabolic parameters were evaluated by analysis of variance testing the effects of group, time, and interaction between group and time. Postoperative ventricular function was analyzed by analysis of covariance. Statistical significance was assumed at a probability level of less than 0.05. Data were reported as the mean ± standard error of the mean in the text and figures.

Results

Preliminary alpha-tocopherol dose-response study. In the first part of the study a dosage of 100 mg given orally every day for 14 days did not result in a statistically significant elevation of total alpha-tocopherol (Fig. 1) or D3-alpha-tocopherol (Fig. 2) myocardial concentrations. When patients were given 300 mg a day for 14 days, myocardial levels of total alpha-tocopherol (deuterated plus nondeuterated) were increased twofold over levels in the placebo control group ($p < 0.05$) (Fig. 1). The increase in total alpha-tocopherol levels was due to the administered deutrium-labeled alpha-tocopherol (Fig. 2). Increasing the daily dose of alpha-tocopherol to 900 mg did not further increase myocardial levels. No deuterated alpha-tocopherol was detected in the myocardial tissue of the patients receiving the corn oil placebo. A decrease ($p < 0.05$) in myocardial alpha-tocopherol levels was noted at the onset of reperfusion (crossclamp removal) in the patients receiving 300 and 900 mg of alpha-tocopherol. By 20 minutes of reperfusion the myocardial alpha-tocopherol levels had returned to preoperative levels.

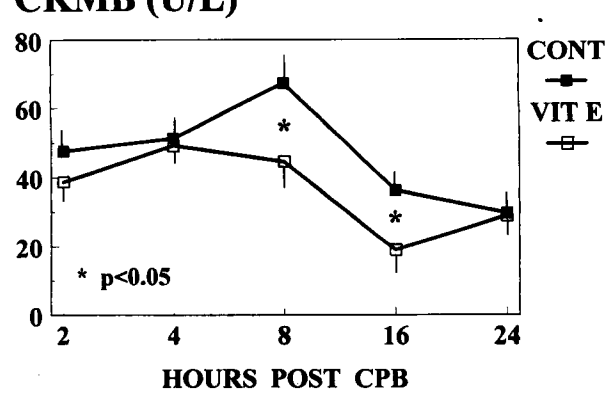

Fig. 6. Arterial CK-MB activity was greater in the placebo control than the alpha-tocopherol–treated patients ($p < 0.05$ by analysis of variance). The differences were greatest 8 and 16 hours after the operation ($p < 0.05$ by Duncan's test).

Double-blind randomized trial. No differences in age, functional class, ejection fraction, number of diseased vessels, number of bypass grafts, crossclamp time, or pump time were observed between the patients in the placebo group and those treated with vitamin E (alpha-tocopherol) (Table I).

Myocardial oxygen consumption, coronary sinus blood flow, and myocardial lactate production were similar between the tocopherol-treated patients and placebo control patients after crossclamp release, during reperfusion on bypass, and after discontinuation of cardiopulmonary bypass.

During atrial pacing on bypass, 25 minutes after crossclamp release, lactate extraction, expressed as percent change from baseline, decreased ($p < 0.05$) in control patients and increased in patients receiving alpha-tocopherol (Fig. 3); the difference was statistically significant ($p < 0.05$). During bypass, coronary sinus blood flow increased similarly in both groups with atrial pacing. Myocardial oxygen consumption increased with atrial pacing in both groups and was not different between treatment and placebo control groups (Fig. 4). After bypass was discontinued, atrial pacing was done again. Coronary sinus blood flow declined in control patients but increased in alpha-tocopherol–treated patients (percentage of baseline flow; control −5% ± 7%, tocopherol +82% ± 25%, $p = 0.01$). Neither oxygen consumption nor lactate extraction was different between tocopherol-treated and placebo control patients. No differences in metabolic parameters were noted when pacing was performed in the intensive care unit 4 hours after the operation.

Postoperative end-systolic elastance (the relation between end-systolic pressure and end-systolic volume indices) tended to be greater in the tocopherol-treated patients, but the difference was not significantly different ($p = 0.08$). Left ventricular stroke work indices were higher in the tocopherol-treated patients 4 hours after the operation (tocopherol, 27 ± 2 mm Hg ml/m^2; control 14 ± 4 mm Hg ml/m^2; $p = 0.017$) at similar end-diastolic volume indices (tocopherol, 50 ± 5 ml/m^2; control 43 ± 4 ml/m^2; $p = 0.33$), indicating a greater preload recruitable stroke work index ($p = 0.02$). Diastolic compliance was increased 4 hours after the operation in the alpha-tocopherol–treated patients (Fig. 5) ($p = 0.045$ by analysis of covariance).

Postoperative CK-MB values were higher in the placebo control patients than the tocopherol-treated patients ($p < 0.05$ by analysis of variance) (Fig. 6). Eight and 16 hours after discontinuation of cardiopulmonary bypass, CK-MB levels were significantly less ($p < 0.05$) in the tocopherol-treated patients than in the control patients. This difference was no longer apparent 24 hours after the operation.

Discussion

Oxygen-derived free radicals may contribute to postoperative myocardial metabolic and functional abnormalities despite apparently adequate cold blood cardioplegia.[4, 8] The proteins[2] and the phospholipids of the sarcolemma[4, 5] are the primary targets of free radical lipid peroxidation. Alpha-tocopherol is the major, and perhaps the only, lipid-soluble chain-breaking antioxidant in the sarcolemma.[6, 7] Therefore increasing cardiac alpha-tocopherol concentrations may reduce sarcolemmal injury and improve myocardial metabolic and functional recovery.

Alpha-tocopherol is biologically the most active of the four tocopherols that together constitute "natural" vitamin E, and the RRR stereoisomer is the most biologically active of the eight stereoisomers that together constitute synthetic, all-racemic alpha-tocopherol. In the preliminary dose-response study, 300 mg of RRR-alpha-tocopherol a day orally for 2 weeks before the operation doubled the cardiac concentrations. A dose of 100 mg a day for 2 weeks increased the cardiac levels of alpha-tocopherol, but the increase was not statistically greater than that in the control subjects. However, the statistical power of our preliminary study was insufficient to conclusively state that 100 mg a day for 2 weeks did not increase cardiac tocopheral levels. Tripling the dose to 900 mg a day for 2 weeks did not further increase the myocardial levels more than 300 mg a day. Additional alpha-tocopherol was probably not absorbed in the gastrointestinal tract. Myocardial uptake of alpha-tocopherol was slow compared with its uptake in the lungs in rats.[13] The half-life of alpha-tocopherol was 23 days in the rat myocardium but only 7 days in the lungs.[13] The reason for the slow uptake and turnover in the myocardium is unclear.

In the preliminary dose-response study, the patients receiving 300 and 900 mg of RRR-alpha-tocopherol had a small but significant ($p < 0.05$) depression of myocardial alpha-tocopherol levels at crossclamp removal, with recovery at 20 minutes of reperfusion. This decrease of tocopherol in the sarcolemma may reflect a burst of oxyradicals and formation of phospholipid conjugated dienes (the chemical signature of oxyradical-derived injury) in the myocardium with reperfusion.[4, 5] Unfortunately, conjugated dienes were not measured in this study because of the complexity of our human protocol and the difficulty in accurately measuring conjugated dienes. The partial return of the alpha-tocopherol levels after 20 minutes of reperfusion may be explained by reduction of the tocopheroxyl radical by aqueous antioxidants such as ascorbic acid and glutathione or by enzymatic reduction of the tocopheroxyl radical to alpha-tocopherol, as postulated by Packer and colleagues.[20]

The double-blind randomized trial was designed to detect subtle improvements in myocardial metabolism and ventricular function after elective coronary bypass operations. We[12] have previously reported that a terminal warm cardioplegic infusion increased myocardial lactate extraction ($p < 0.05$) and resulted in greater postoperative diastolic compliance ($p < 0.05$) than control with 12 patients per group. We[21] also demonstrated increased lactate extraction ($p < 0.05$) and improved systolic function ($p < 0.05$) by increasing arterial lactate concentrations with 10 patients per group. Therefore, we believed that vitamin E would be beneficial in these low-risk patients if it improved the metabolic response to a mild hemodynamic stress and if parameters of postoperative ventricular function were improved.

The myocardial metabolic differences between the control and treated patients were small and transient. Myocardial lactate extraction increased with atrial pacing in patients receiving alpha-tocopherol, and lactate production was found with atrial pacing in the control group. However, after bypass no differences were found in the metabolic response to this mild hemodynamic stress. This lack of difference suggests restoration of myocardial metabolism in both groups. Myocardial oxygen consumption was not different between the two groups after the operation. However, the imprecision of

thermodilution blood flow measurements resulted in high variability of oxygen consumption estimates. Our technique of measuring myocardial oxygen consumption may not be sufficiently sensitive to detect small changes in aerobic metabolism.

Left ventricular stroke work indices were higher in the tocopherol group at similar ventricular volumes, suggesting increased preload recruitable stroke work. The tocopherol-treated patients had lower diastolic pressures at similar ventricular volumes than the control patients, which suggests greater diastolic compliance. We have previously associated greater diastolic compliance in the early postoperative period with improved aerobic metabolism and enhanced myocardial protection.[11, 12, 21]

The subtle improvements in myocardial metabolism, ventricular function, and the decrease in CK-MB release was statistically but not clinically significant. Therefore, oral vitamin E cannot be recommended for patients having elective coronary bypass operations. However, vitamin E may be beneficial for high-risk patients such as those who require urgent coronary revascularization for unstable angina.[22, 23] These patients probably have greater free radical reperfusion injury and may benefit more from antioxidant therapy. A prospective randomized trial will be required to demonstrate a clinically relevant benefit from preoperative vitamin E therapy. Unfortunately, oral administration of antioxidants may require 2 weeks to double myocardial concentrations. We[24, 25] have demonstrated that an infusion of a water-soluble analog of vitamin E could significantly reduce infarct size in an animal model of ischemia and reperfusion. Water-soluble vitamin E analogs offer the promise of myocardial salvage for patients with acute ischemia. However, controlled clinical trials will be required to demonstrate their efficacy.

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