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Hypertension Prophylaxis With Omega-3 Fatty Acids in Heart Transplant Recipients

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Objectives. **This study sought to determine whether omega-3 fatty acids act as hypertension prophylaxis in heart transplant recipients and have an impact on vascular reactivity.**

Background. **Cyclosporine-induced hypertension is probably related to endothelial dysfunction. Suggested vasodilatory mechanisms of omega-3 fatty acids may therefore be particularly beneficial in heart transplant recipients.**

Methods. **Heart transplant recipients were randomized to receive either 4 g of omega-3 fatty acids (treatment group, n = 14) daily or corn oil (placebo group, n = 14) from the fourth postoperative day. Twenty-four hour blood pressure monitoring was performed at day 12 and 1, 2, 3 and 6 months postoperatively. Microvascular endothelium-dependent vasodilation, evaluated by skin laser Doppler perfusion measurements of postocclusive reactive hyperemia, was determined preoperatively and at the end of the study.**

Results. **With comparable characteristics at the time of randomization, blood levels of cyclosporine did not at any point differ between the groups. After 6 months, systolic blood pressure decreased 2 ± 4 mm Hg (mean ± SEM) in the treatment group and increased 17 ± 4 mm Hg in the placebo group ($p < 0.01$), whereas diastolic blood pressure increased 10 ± 3 and 21 ± 2 mm Hg ($p < 0.01$), respectively. The decrease in systolic blood pressure was inversely proportional to increases in concentrations of serum eicosapentaenoic and docosahexaenoic acid ($p = 0.01$). After 6 months, five patients in the treatment group and nine in the placebo group needed additional antihypertensive treatment. Although the endothelial-dependent phase of the reactive hyperemic response remained unchanged in the treatment group, it decreased significantly in the placebo group.**

Conclusions. **Postoperative daily administration of 4 g of omega-3 fatty acids in heart transplant recipients is effective as hypertension prophylaxis, depending on increases in serum eicosapentaenoic and docosahexaenoic acids. Preservation of microvascular endothelial function, demonstrated by a more pronounced response to forearm skin ischemia in the treatment group, may contribute to the hypotensive role of omega-3 fatty acids.**

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Hypertension is a common complication in cyclosporine treatment. In heart transplant recipients it is present among 60% to 100% of patients (1), and optimal control is often difficult to achieve. Evident within a few weeks postoperatively, it is characterized by normal central hemodynamic variables and increased systemic vascular resistance. The underlying mechanisms of peripheral vasoconstriction are unknown, but recent reports suggest (2–5) a dysfunctional endothelium with an imbalance of local mediators of vasoconstriction and vasodilation.

Omega-3 fatty acids have favorable metabolic effects that may protect against cardiovascular disease. Evidence of improved vascular reactivity, due to changes in the prostanoid profile or enhanced release of nitric oxide (6,7), suggests particular usefulness in cyclosporine-induced hypertension. Although a hypotensive effect has been questioned, two recent meta-analyses (8,9) indicate a significant but modest effect on blood pressure in hypertensive patients. A recent study (10) in hypertensive heart transplant recipients treated with omega-3 fatty acids for 12 weeks also demonstrated a significant reduction in blood pressure.

We therefore performed a randomized, double-blind, placebo-controlled study to assess whether prophylactic administration of omega-3 fatty acids prevents hypertension in cyclosporine-treated heart transplant recipients. To improve the accuracy and provide additional information on the diurnal pattern of blood pressure, the effect was evaluated by 24-h ambulatory monitoring. The impact of omega-3 fatty acids on endothelium-dependent vasodilation was assessed by examination of the postocclusive hyperemic response.

Methods

Patients. Thirty consecutive orthotopic heart transplant recipients were randomized to receive either 4 capsules/day of highly concentrated ethyl esters of omega-3 fatty acids (Omacor, Pronova AS, Oslo, Norway) (treatment group) or an equal

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Abbreviations and Acronyms
HDL = high density lipoprotein
LDL = low density lipoprotein

amount of an ethyl ester of corn oil (placebo group). The soft gelatin capsule in the treatment group contains 1 g of fatty acids (46.5% eicosapentaenoic acid and 37.8% docosahexaenoic acid), whereas 3.7 mg of alpha-tocopherol as antioxidant was added to both the active treatment and placebo capsules. All patients gave written informed consent. They were instructed to refrain from cod-liver oil during the study, which was approved by the Regional Ethics Committee.

Treatment was started 4 days postoperatively and continued for 6 months. Compliance was ascertained by capsule counts and determination of serum phospholipid fatty acids. All the patients received a triple immunosuppressive regimen of cyclosporine, azathioprine and prednisolone. Cyclosporine was initiated immediately preoperatively at a dose of 6 mg/kg body weight and tapered off according to the department rejection protocol. Azathioprine was given at 2 mg/kg per day and prednisolone at 0.2 mg/kg per day and tapered off to 0.1 mg/kg per day over 2 months. Rejection was treated with boluses of methylprednisolone (Solu-Medrol, Pharmacia & Upjohn, Puurs, Belgium) and, if necessary, rabbit anti-thymocyte globulin (Thymoglobuline, Pasteur Merieux, Lyon, France).

Blood pressure monitoring. Twenty-four hour blood pressure monitoring was performed with an Accutracker 2, Suntech model 104 device (Suntech Medical Instruments) using the R wave gated auscultatory method. Blood pressure was measured four times every hour during the day (7 AM to 11 PM) and twice every hour during the night (11 PM to 7 AM). Eighty readings were attempted during each recording session. The average number of readings accepted for evaluation was equal in the two groups and fell from 95% to 88% during follow-up, probably reflecting more disturbances from increasing physical activity. Two recording sessions with >20% technical errors were excluded. Recordings were analyzed by personal computer (Accusoft, Suntech Medical Instruments).

Each patient underwent 24-h measurements at day 12 and 1, 2, 3 and 6 months postoperatively. Recordings earlier than day 12 were complicated by the unstable postoperative state and the extensive use of pacemakers, the latter preventing simultaneous blood pressure monitoring with the ambulatory device. As reference values, we adopted the mean 24-h systolic and diastolic limits proposed by the meta-analysis of Staessen et al. (11), and patients with probable hypertension (>139/87 mm Hg for 24 h) were considered for antihypertensive treatment with enalapril. In these patients, medication was withheld for 48 h before the next recording and discontinued if the recording was normotensive due to the unstable postoperative hemodynamic situation and the possible accumulating hypotensive effect of omega-3 fatty acids.

Changes in blood pressure load were derived from the area under the mean arterial blood pressure curve at day 12 and 6 months postoperatively. The day and night periods were computed separately and combined to form the 24-h area under the curve. Threshold values used for calculation were 107 and 93 mm Hg for day and night, respectively, derived from systolic and diastolic values of 140/90 and 120/80 (one third of the pulse pressure added to the diastolic blood pressure).

Measurements of reactive hyperemia. Skin-reactive hyperemia was determined using a laser Doppler flowmeter (Periflux, model PF3, Perimed Ltd., Järfälla, Sweden) (12), which produces a voltage signal proportional to microvascular perfusion (13). After 20 min of acclimatization in a quiet room with constant air temperature (22 ± 1°C), laser Doppler perfusion measurements were performed on the pulp of the left third finger with the patients in a supine position. Digital skin temperature was recorded with an electronic thermometer (Grant Instruments, Cambridge, UK). After measurement of basal perfusion, 3 min of suprasystolic pressure occlusion (280 mm Hg) of the left forearm was followed by a sudden release of the cuff. Rest perfusion level, peak hyperemic response and duration of reactive hyperemia were recorded (Fig. 1). In addition, perfusion debt repayment was also calculated, defined as the area under the perfusion curve versus time until return of the signal to preocclusion baseline levels.

Laboratory evaluations. Trough levels of cyclosporine were determined by a fluorescence polarization immunoassay method 12 h after the last dose of the drug. Serum lipids were determined after overnight fasting before the start and at the end of the study. Total cholesterol and triglycerides were analyzed by standard enzymatic calorimetric methods, whereas high density lipoprotein (HDL) cholesterol was determined in the supernatant after precipitation with phosphotungstic acid and magnesium chloride. The phospholipid acids were quantified by gas chromatography. Creatinine clearance was measured before and 6 months after transplantation.

Statistics. Data are expressed as mean value ± SEM. One-way analysis of variance with repeated measurements was used for multiple intragroup analysis. Multivariate analysis of variance followed by the Newman Keuls test was used for multiple time comparisons between the two groups. The Mann-Whitney *U* test was applied for unpaired statistical analysis and Wilcoxon signed-rank test for paired results. The Pearson correlation test was used for correlation analysis. A value <0.05 was considered statistically significant.

Results

Patients. Of the 30 patients who entered the study, 14 in each group were studied for 6 months. One patient in each group died of vascular rejection 7 and 8 weeks postoperatively and were therefore excluded from the total analyses. There were no significant differences between the two groups for any of the recorded characteristics (Table 1). One patient in the treatment group and three in the placebo group experienced

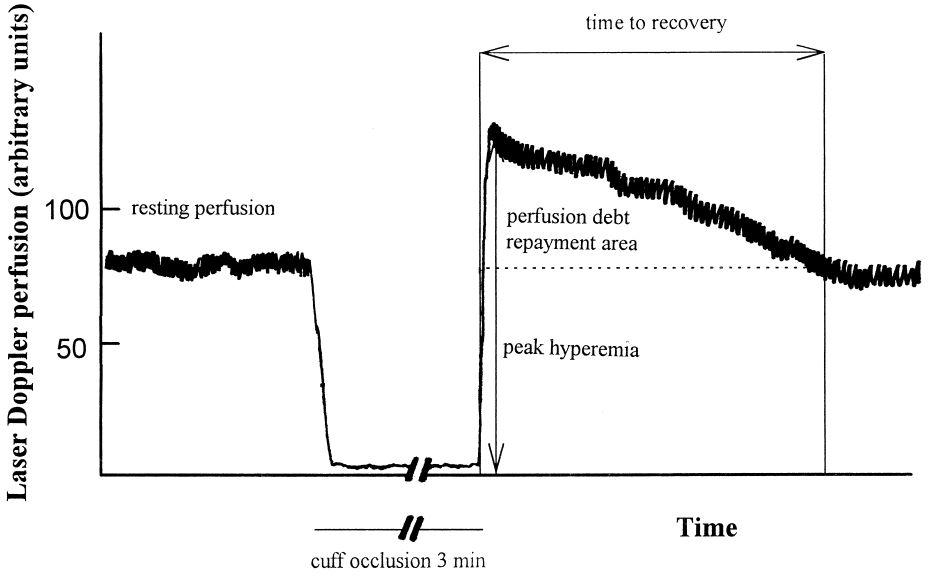

Figure 1. Representative example of postocclusive reactive hyperemia taken from a continuous recording using laser Doppler perfusion measurements.

minor strokes. The gelatin capsules were well tolerated, and mild abdominal complaints were comparable between the groups.

Blood pressure. Twenty-four hour blood pressure measurements at baseline were higher in the treatment group than in the placebo group (134/73 ± 5/3 vs. 126/70 ± 5/2 mm Hg, respectively, $p < 0.05$ for systolic blood pressure). In the treatment group, a slight fall in systolic values of 2 ± 4 mm Hg and a diastolic increase averaging 10 ± 3 mm Hg was observed from baseline to 6 months postoperatively. By contrast, a significant and consistent increase in mean systolic and diastolic blood pressure at all time intervals took place in the placebo group, averaging 17 ± 4/21 ± 2 mm Hg from baseline to 6 months postoperatively; both changes were significantly higher ($p < 0.01$) than in the placebo group (Fig. 2). Except for changes in diastolic blood pressure at 1 month, the increase in both systolic and diastolic blood pressure was significantly lower at each 24 h registration in the treatment group ($p < 0.01$).

Figure 3 shows the 24-h mean arterial blood pressure profiles of the two groups at baseline and at 6 months. The placebo group reveals a greater and more persistent increase in 24-h blood pressure after 6 months. The calculated increase in the 24-h hypertensive load from baseline to 6 months, estimated as changes in the area under the mean arterial blood pressure curves with threshold values for hypertension as indicated in Figure 3, was also significantly lower in the treatment group (60 ± 28 vs. 149 ± 35 mm Hg, $p < 0.05$). The higher blood pressure in the treatment group at baseline was due to a less pronounced nocturnal dip and a steeper rise in the early morning hours. The percent nocturnal reductions in systolic and diastolic blood pressure were 1 ± 2% and 6 ± 3% in the treatment group and 7 ± 2% and 8 ± 3% in the placebo group, respectively. The corresponding nocturnal reductions after 6 months were 11 ± 2% and 14 ± 4% versus 8 ± 3% and 9 ± 3%, respectively. The attenuated rise in blood pressure in the treatment group was observed throughout the 24-h period after 6 months.

After 6 months, five patients in the treatment group and nine in the placebo group needed additional antihypertensive treatment. Using the 24-h blood pressure criteria mentioned earlier, the mean treatment group blood pressure values of 135/85 ± 5/4 mm Hg were within normotensive limits, whereas 140/89 ± 4/3 mm Hg in the placebo group indicates systolic and diastolic hypertension.

Reactive hyperemia. Three patients underwent heart transplantation before preoperative reactive hyperemia could be

Table 1. Characteristics of Recipients and Donors in the Two Study Groups

	Placebo Group (n = 14)	Treatment Group (n = 14)
Donor		
Age (yr)	33 ± 3	29 ± 2
% male	85	73
Cold ischemic time (min)	121 ± 11	96 ± 18
Warm ischemic time (min)	52 ± 5	55 ± 6
Recipient		
Age (yr)	53 ± 6	48 ± 10
% male	73	73
Body mass index (kg/m^2)	23.3 ± 0.7	24.2 ± 0.8
Creatinine clearance (ml/min)	55 ± 4	57 ± 5
Previous hypertension (no. of pts)	4	3
Etiology of HF (no. of pts)		
Cardiomyopathy	3	5
Coronary heart disease	11	9

Data presented are mean value ± SEM, unless otherwise indicated; no significant differences were found between the groups. HF = heart failure; pts = patients.

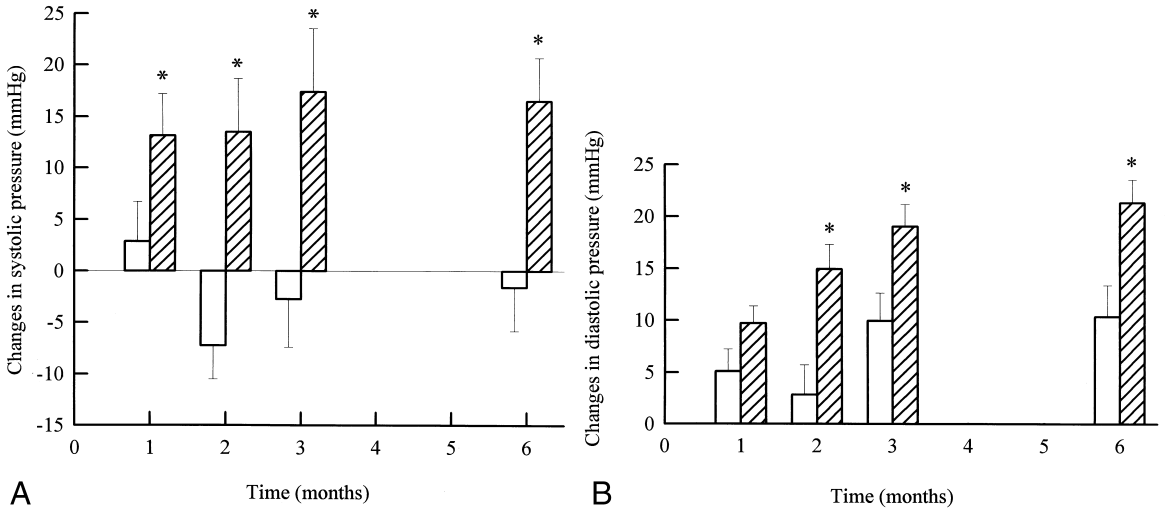

Figure 2. Mean changes in 24-h systolic **(A)** and diastolic blood pressure **(B)** compared with 24-h measurements at day 12 postoperatively in heart transplant recipients treated with omega-3 fatty acids (**open bars,** n = 14) or placebo (**hatched bars,** n = 14). *p < 0.01.

measured. Before transplantation, the levels of skin rest perfusion, peak reactive hyperemia, time to recovery from the hyperemic response and the perfusion debt repayment area did not differ between the two groups (Table 2). Skin temperature at this point and at 6 months postoperatively was also similar (treatment group vs. placebo group: 32.3 ± 0.4 vs. 31.0 ± 0.8°C and 32.8 ± 0.4 vs. 33.2 ± 0.5°C, respectively). Peak hyperemic levels were significantly improved in both groups 6 months postoperatively. However, whereas the time required for the hyperemic perfusion to return to preocclusive levels increased slightly in the treatment group (70.2 ± 13.3 vs. 74.7 ± 10.5 s), this phase decreased in the placebo group (75.3 ± 11.1 vs. 43.0 ± 6.7 s, $p < 0.05$). Accordingly, the hyperemic perfusion, determined by the area of the postocclusion perfusion tracing, was significantly higher in the treatment group (1,867 ± 350 vs. 3,310 ± 52 arbitrary units-s, $p < 0.05$). No significant relation was found between changes in the hyperemic response and those in systolic blood pressure ($r = -0.23$, $p = 0.3$).

Figure 3. Twenty-four hour mean arterial blood pressure 12 days and 6 months after heart transplantation in the treatment (n = 14) **(A)** and placebo (n = 14) **(B)** groups. Each **circle** represents a group mean, with **vertical bars** indicating SEM. Threshold values **(dashed lines)** of 107 mm Hg during the day and 93 mm Hg during the night were used to determine area under the blood pressure curve, reflecting the hypertensive load.

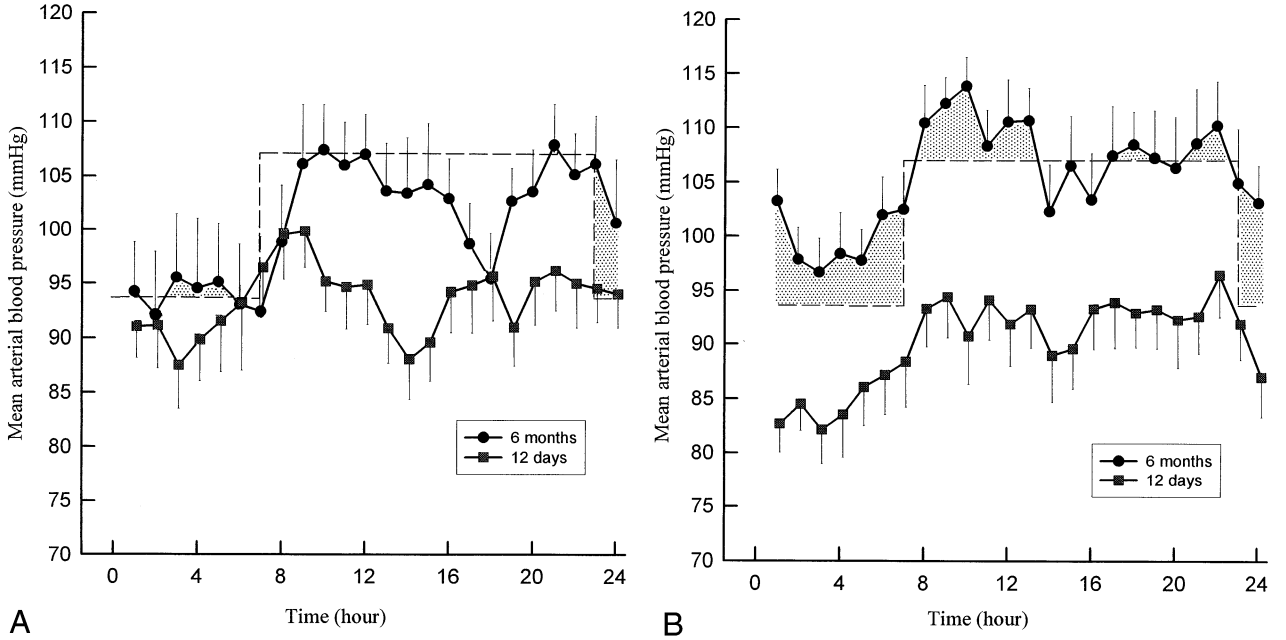

Table 2. Reactive Hyperemic Response Before and 6 Months After Heart Transplantation

	Placebo Group (n = 12)		Treatment Group (n = 13)	
	Before Tx	6 mo After Tx	Before Tx	6 mo After Tx
Rest perfusion (AU)	58 ± 9	89 ± 9	71 ± 8	78 ± 9
Peak hyperemia (AU)	99 ± 9	141 ± 10*	101 ± 9	124 ± 6*
Time to recovery (s)	75.3 ± 11.1	43.0 ± 6.7*	70.2 ± 13.3	74.7 ± 10.5†
Perfusion debt repayment area (AU)	3,146 ± 670	1,867 ± 350‡	3,447 ± 741	3,310 ± 520†

*$p < 0.05$, ‡$p < 0.01$ versus preoperative values. †$p < 0.05$ versus 6-month placebo group value. Data presented are mean value ± SEM. AU = arbitrary units; Tx = transplantation.

Laboratory values. The mean concentration of serum phospholipid omega-3 fatty acids increased significantly in the treatment group and remained unchanged in the placebo group (Table 3). Triglycerides were significantly reduced in the treatment group, whereas a significant increase in total cholesterol and HDL cholesterol occurred in both groups. The relation between the change in 24-h blood pressure and that in serum phospholipids was studied in the treatment group. The changes in 24-h systolic blood pressure were significantly related to those in eciosapentaenoic and docosahexaenoic acid taken together ($r = -0.69$, $p = 0.01$) (Fig. 4). In contrast, we were unable to demonstrate a significant relation between changes in the hyperemic response and changes in eicosapentaenoic and docosahexaenoic acid ($r = 0.21$, $p = 0.3$). Creatinine clearance improved in both groups, with an insignificantly higher value in the treatment group (81 ± 5 ml/min) than in the placebo group (74 ± 8 ml/min) by the end of the study. The dose and trough concentration of cyclosporine and the dose of prednisolone were not different at any time between the groups (Table 4).

Table 3. Serum Phospholipid Fatty Acids and Lipids Before and 6 Months After Heart Transplantation

	Placebo Group (n = 14)		Treatment Group (n = 14)	
	Before Tx	6 mo After Tx	Before Tx	6 mo After Tx
Fatty acid (mg/liter)				
EPA	38 ± 6	43 ± 8	27 ± 6	100 ± 10*†
DHA	105 ± 10	121 ± 10	77 ± 7‡	130 ± 7*
Total cholesterol (mg/dl)	208 ± 19	290 ± 16*	193 ± 15	247 ± 16*
HDL cholesterol (mg/dl)	32 ± 4	52 ± 4*	30 ± 3	52 ± 5*
Triglycerides (mg/dl)	183 ± 11	197 ± 31	181 ± 29	124 ± 27†§

*$p < 0.01$, §$p < 0.05$ versus preoperative values. †$p < 0.05$ versus 6-month placebo group value. ‡$p < 0.05$ versus preoperative placebo group value. Data presented are mean value ± SEM. DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HDL = high density lipoprotein; Tx = transplantation.

Discussion

Effects on blood pressure. Our study confirms previous observations that most heart transplant recipients treated with cyclosporine develop hypertension within 6 months postoperatively. Sequential 24-h ambulatory measurements during this period revealed a consistent increase in blood pressure in the placebo group. Systolic and diastolic blood pressure reached levels of probable hypertension (11), and most patients needed antihypertensive drug treatment. By the end of the study, the hypotensive effect attributable to treatment with omega-3 fatty acids was 19 mm Hg in systolic and 11 mm Hg in diastolic blood pressure. Comparable to other studies in transplant recipients (10,14), our results seem to exceed those obtained in treatment with omega-3 fatty acids in essential hypertension (8,9). Three of the five patients in need of antihypertensive drug treatment demonstrated an increase in serum levels of eicosapentaenoic and docosahexaenoic acid below the group means. We also found a significant inverse relation between the development of systolic hypertension and the increase in serum omega-3 fatty acids. Bønaa et al. (15) also observed a

Figure 4. Relation between changes in systolic blood pressure and in serum eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) during treatment with omega-3 fatty acids.

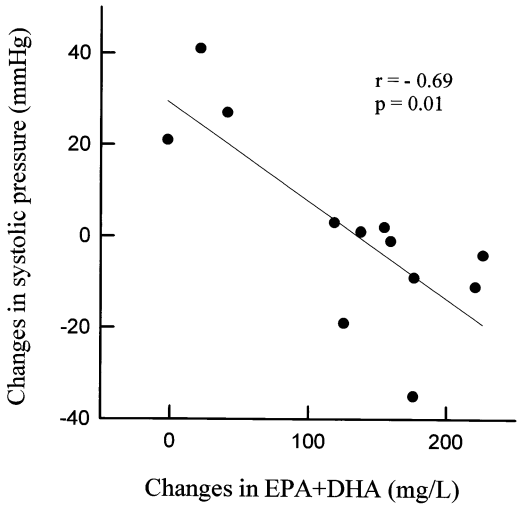

Table 4. Cyclosporine Doses/Trough Values and Prednisolone Doses

	Cyclosporine Dose (mg/kg body weight)		Cyclosporine Concentration (ng/ml)		Prednisolone Dose (mg/kg body weight)	
Time After Tx	Placebo Group	Treatment Group	Placebo Group	Treatment Group	Placebo Group	Treatment Group
12 days	5.5 ± 0.4	5.1 ± 0.3	341 ± 19	342 ± 12	0.2 ± 0.0	0.2 ± 0.0
1 mo	4.8 ± 0.3	5.0 ± 0.4	368 ± 15	348 ± 22	0.2 ± 0.0	0.2 ± 0.0
2 mo	4.7 ± 0.2	4.0 ± 0.2	294 ± 10	290 ± 15	0.1 ± 0.0	0.1 ± 0.0
3 mo	4.1 ± 0.2	4.3 ± 0.2	265 ± 12	230 ± 16	0.1 ± 0.0	0.1 ± 0.0
6 mo	3.5 ± 0.2	3.7 ± 0.3	183 ± 5	190 ± 11	0.1 ± 0.0	0.1 ± 0.0

Data presented are mean value ± SEM. Tx = transplantation.

similar relation for mean arterial pressure and omega-3 fatty acids in their successful treatment of mild hypertensive patients. Although relatively few patients were studied, it is conceivable that the observed reductions in blood pressure depend on the increases in serum omega-3 fatty acids, also among heart transplant recipients.

The differences in 24-h blood pressure between the two groups observed at baseline were probably due to the relatively few patients studied and is supported by the fact that patient characteristics, cyclosporine dose and blood concentrations were equal and that there were no clear reasons for an initial blood pressure increase caused by treatment with omega-3 fatty acids.

There are somewhat conflicting data concerning the 24-h profile of blood pressure in heart transplant recipients. Early reports (16,17) suggested a blunted decline or even a rise in nocturnal values. Our results agree with a normalization of the circadian rhythm of blood pressure variability within months after heart transplantation (18,19). The 24-h mean arterial blood pressure profiles after 6 months show a reduction in blood pressure load in the treatment group during both day and night.

Reactive hyperemia and possible hypotensive mechanisms of omega-3 fatty acids. Although the origin of cyclosporine-induced hypertension may be multifactorial, recent reports (2–5) suggest the vascular endothelium as the main site of impaired vascular regulation. The reactive hyperemic response has been shown (20) to depend on intact endothelial function with an adequate production of vasoactive substances. Thus, the flow-dependent vasodilation of human conduit arteries assessed by a high precision echocardiographic Doppler device has been suggested (21) as a reliable noninvasive test of endothelial function. Applied in patients with severe heart failure, the hyperemic response of radial artery and total forearm blood flow is impaired (22,23). In our study, the peak hyperemic responses improved significantly in both groups after heart transplantation. However, although the treatment group maintained the preoperative levels, both the duration of the hyperemia and the perfusion debt repayment decreased significantly in the placebo group. This finding is consistent with our earlier finding (24) of lower perfusion values at the mid to late phase of hyperemia during long-term follow-up in heart transplant recipients. Detectable within 6 months postoperatively, these results oppose data that demonstrate reversible abnormal endothelium-dependent responses in heart failure after transplantation (25). Despite normalization of cardiac output and decreased vascular and interstitial edema, an otherwise withdrawal of vasoconstrictor tone might be antagonized by cyclosporine.

In vitro models and animal studies of cyclosporine toxicity (4,5) have found evidence of inhibition of nitric oxide–mediated vasodilation. Two recent studies (21,26) used N^G-monomethyl-L-arginine, a selective blocker of nitric oxide synthesis, before cuff occlusion, to examine the contribution of nitric oxide in human reactive hyperemia. Both studies demonstrated that peak hyperemia was of comparable levels, with or without the blocker. However, significantly lower blood flow levels at mid to late phases of the response resulted in significantly lower flow debt repayment in the N^G-monomethyl-L-arginine group. Thus, when these results are compared with those of our placebo group, cyclosporine-treatment offers similarities to the N^G-monomethyl-L-arginine group in that maintainance of vasodilation is impaired. Furthermore, treatment seems to counteract these responses, indicating endothelial dysfunction. Fleischhauer et al. (27) improved endothelial-dependent vasodilatory response in coronary arteries of heart transplant recipients receiving cyclosporine after supplementation with omega-3 fatty acids, most likely due to increased release or activity of nitric oxide. Although our study also indicates an improvement in endothelial function and a hypotensive role of omega-fatty acids, we were unable to find a significant correlation between improvement in endothelial function and changes in serum levels of omega-3 fatty acids or blood pressure. It remains uncertain whether lack of such interrelation reflects our way of addressing endothelial function or whether omega-3 fatty acids possess other undetected qualities of lowering blood pressure.

Cyclosporine therapy seems to induce changes in the prostaglandin profile, increasing the production of the vasoconstrictor tromboxane A_2 (28). In contrast, supplementation with omega-3 fatty acids increases tromboxane A_3 formation, coinciding with a fall in tromboxane A_2 together with a significant increase in total prostacyclin levels, promoting a vasodilatory effect (6). In two recent randomized, double-blind studies of treatment with omega-3 fatty acids in 10 hypertensive heart transplant recipients (10) and 33 cyclosporine-treated renal

transplant recipients (14), a significant reduction in blood pressure was achieved, and a possible beneficial change in the prostaglandins was discussed. Although prostaglandins were not actually measured in either of these studies, a possible omega-3 fatty acid–induced vasodilation due to an improved prostaglandin profile has been demonstrated in cyclosporine-treated animals (29).

Because prostaglandins are endothelial factors that may also regulate the mid to late phases of reactive hyperemia in humans, although controversial findings exist (21,30), our technique (without the preocclusive introduction of blocking agents) is inadequate in determining the relative impact of prostaglandins with nitric oxide. The hypotensive mechanisms suggested are not mutually exclusive. The physiologic changes induced may result from simultaneous operating factors, with a net result of peripheral vasoconstriction due to endothelial dysfunction. Other local vasoactive substances, such as adenosine and adenosine triphosphate–sensitive potassium channels, also seem to be involved in the reactive hyperemia (31,32) and may play a significant role in altering the response. However, we are unaware of studies dealing with interaction of these factors with cyclosporine. Furthermore, a history of heart failure and hypercholesterolemia might add to the development of endothelial damage, otherwise induced by cyclosporine. The multifactorial background of damage to the endothelium leads to the potential application of omega-3 fatty acids in these patients, supported by our finding of a hypotensive effect exceeding that obtained in subjects with essential hypertension (8,9).

Because of strong evidence of lipoproteins modulating vascular reactivity (33), the improved endothelial-dependent responses could be due to the lower levels of triglycerides in the treatment group. However, although the reduction of triglycerides with omega-3 fatty acids is well known, it is only lowering of total or low density lipoprotein (LDL) cholesterol that has a documented impact on endothelial function (34). Chin and Dart (35) compared the lipid-lowering effect of hydroxymethylglutaryl-coenzyme A reductase inhibition with daily supplementation of 5.75 g of omega-3 fatty acids in hypercholesterolemic subjects. The statin reduced LDL cholesterol by nearly 40% and significantly improved the response to endothelium-dependent relaxation. Restoration of endothelial function was also demonstrated in the omega-3 fatty acids group, despite unchanged levels of cholesterol and triglycerides after only 4 weeks treatment. Thus, taking these results into account with the fact that omega-3 fatty acids did not lower cholesterol concentrations in our study, the hypotensive effect is probably not linked to the reduction in triglycerides.

Conclusions. Prophylactic supplementation with 4 g daily of omega-3 fatty acids lowers blood pressure in heart transplant recipients, depending on increases in serum eicosapentaenoic and docosahexaenoic acids. Improved vascular reactivity in the treatment group, demonstrated by a more pronounced response to forearm skin ischemia than in the placebo group, indicates an endothelial protective effect that may contribute to the hypotensive role of omega-3 fatty acids.

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