

# Omega-3 fatty acids improve blood pressure control and preserve renal function in hypertensive heart transplant recipients

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**Background** Hypertension and cyclosporine-induced nephrotoxicity are common complications in heart transplant recipients. Omega-3 fatty acids may prevent blood pressure rise early, but have not been studied long-term after heart transplantation.

**Methods and Results** Forty-five clinically stable hypertensive heart transplant recipients were studied 1–12 years after transplantation and randomized in a double-blind fashion to receive either 3.4 g of omega-3 fatty acids daily or placebo for 1 year. Ambulatory 24 h blood pressure monitoring and haemodynamic studies were performed before randomization and at the end of the study. Systolic blood pressure increased by  $8 \pm 3$  mmHg ( $P < 0.01$ ) in the placebo group, with a non-significant increase in diastolic blood pressure of  $3 \pm 2$  mmHg ( $P = 0.10$ ), accompanied by a 14% increase in systemic vascular resistance ( $P < 0.05$ ). In contrast, no change in blood pressure or systemic vascular

resistance was recorded in the omega-3 group. Plasma creatinine increased ( $P < 0.01$ ) and glomerular filtration rate decreased ( $P < 0.05$ ) in the placebo group, while no changes were observed in the omega-3 group. The antihypertensive effect was related to an increase in serum eicosapentaenoic and docosahexaenoic acid.

**Conclusion** Treatment with omega-3 fatty acids may reduce the long-term continuous rise in blood pressure after heart transplantation and may offer a direct or indirect renoprotective effect, making these fatty acids a potentially attractive treatment for post-transplant hypertension.

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**Key Words:** Heart transplantation, hypertension, omega-3 fatty acids, kidney, endothelium.

## Introduction

Hypertension is a major complication in cyclosporine-treated heart transplant recipients, occurring in 60–90% of patients within the first postoperative year<sup>[1]</sup>. Heart transplant recipients are characterized by near normal cardiac output, abnormally high systemic vascular resistance, and increasing blood pressure over time despite the use of multiple antihypertensive drugs<sup>[1]</sup>. The mechanism leading to hypertension is not clear, but several factors may be involved. Previous reports suggest that

progressive cyclosporine-induced nephropathy is a major pathogenic mechanism, but endothelial cell mediated effects through a dysbalance between vasoconstrictor and vasodilatory factors may also contribute<sup>[1,2]</sup>.

Omega-3 fatty acids have potentially favourable effects that may protect against cardiovascular disease and reduce mortality in non-transplanted patients<sup>[3]</sup>. They reduce hypertension early after heart transplantation<sup>[4,5]</sup> and in some reports also improve renal function in chronic progressive renal disease<sup>[6]</sup> and kidney graft recipients<sup>[7,8]</sup>. Such observations suggest a role for these fatty acids in the management of cyclosporine-induced hypertension; however, this has not been investigated in heart transplant recipients with established hypertension.

In the present study we hypothesized that omega-3 fatty acids may inhibit the expected rise in blood pressure among hypertensive heart transplant recipients

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**Table 1** Clinical characteristics at baseline among heart transplant recipients who completed the study in both the treatment and placebo groups

	Omega-3 fatty acids (n=21)	Placebo (n=20)
Age (year)	57 ± 2	57 ± 2
Sex (male/female)	20/1	19/1
Body mass index (kg . k <sup>-2</sup> )	26.9 ± 0.8	26.7 ± 0.8
Time after heart transplantation (year)	6 ± 1	6 ± 1
Cyclosporine concentration (µg . ml <sup>-1</sup> )	111 ± 6	117 ± 6
Etiology of heart failure		
Cardiomyopathy	8	9
Coronary heart disease	13	11
Mean 24 h systolic blood pressure (mmHg)	138 ± 3	139 ± 3
Mean 24 h diastolic blood pressure (mmHg)	89 ± 1	90 ± 2
Mean 24 h heart rate (mmHg)	91 ± 2	91 ± 2
Treated hypertension at baseline	17	16
Medication		
Cyclosporine dose (mg . kg <sup>-1</sup> . day <sup>-1</sup> )	2.4 ± 0.1	2.3 ± 0.1
Azathioprine dose (mg . kg <sup>-1</sup> . day <sup>-1</sup> )	1.2 ± 0.1	1.1 ± 0.1
Prednisolone dose (mg . kg <sup>-1</sup> . day <sup>-1</sup> )	0.1 ± 0.01	0.1 ± 0.02
Angiotensin converting enzyme inhibitor	8	9
Calcium antagonist	8	9
Beta-blocker	1	1
Diuretic	6	8
Statin	5	4

Values are mean ± SEM.

long-term after transplantation. This hypothesis was tested in a randomized, double blind, placebo-controlled trial.

## Materials and Methods

### Subjects

Seventy-two consecutive heart transplant recipients were screened for hypertension, using 24 h ambulatory blood pressure monitoring, during annual follow-up from 1997 to 1998. Patients with a 24 h average systolic blood pressure above 139 mmHg or diastolic above 87 mmHg were regarded as hypertensive, as proposed by the meta-analysis of Staessen *et al.*<sup>[9]</sup>. Based on these criteria, 45 heart transplant recipients (43 men and 2 women, mean time after transplantation 6 years, range 1–12) were included in the study. All patients were clinically and haemodynamically stable in New York Heart Association functional class I, without signs of ongoing rejection or significant concomitant disease. The pre-transplant diagnosis was coronary artery disease in 27 (60%) and idiopathic dilated cardiomyopathy in 18 (40%) patients. All received triple-drug-regimen maintenance immunosuppressive therapy with cyclosporine, azathioprine and prednisolone. The majority (n=33) were treated with antihypertensive medication, mainly angiotensin-converting enzyme inhibitors or calcium channels blockers (Table 1). All medication

remained unchanged the 3 months prior to the investigation and throughout the study period.

### Study design

Patients were randomized to take either four capsules/day of highly concentrated ethyl esters of omega-3 fatty acids (Omacor, Pronova AS, Oslo, Norway) (omega-3 group) or an equal amount of ethyl esters of corn oil (placebo group) for 12 months and were stratified according to whether or not they were already receiving antihypertensive medication. The dosage of omega-3 fatty acids were chosen according to previous results in our department early after heart transplantation<sup>[4]</sup>. The soft gelatin capsule in the omega-3 group contained 1 g of fatty acids (46.5% eicosapentaenoic and 37.8% docosahexaenoic), and 3.7 mg of *α*-tocopherol as antioxidant was added to both the active treatment and the placebo capsules. The participants were instructed to refrain from cod-liver oil during the study. The study was approved by the Regional Ethics Committee and all patients gave written informed consent to participation. Compliance was ascertained by capsule counts and determination of serum phospholipid fatty acids.

### Methods

The following procedures were performed at baseline and after 12 months: (i) 24 h ambulatory blood pressure

measurement (see below); (ii) assessment of haemodynamic variables by standard right and left-sided heart catheterization. Mean arterial pressure was determined by the mean of three readings taken at 5 min intervals after 10 min supine rest, using the oscillometric method and a fully automatic blood pressure recorder (Dyapulse 2000 A — Clinical version 3.40, Pulse Metric Inc., San Diego, CA, U.S.A.); (iii) echocardiographic and Doppler variables were obtained by using a System Five instrument (GE Vingmed Ultrasound, Horten, Norway); (iv) endothelium-dependent and -independent vasodilation was ascertained in the skin microcirculation (see below); (v) peripheral blood was sampled. Systemic vascular resistance was calculated according to the following formula:  $[(\text{Mean arterial pressure} - \text{right atrium pressure}) / \text{Cardiac output}] \times 80$ .

### Blood pressure monitoring

Twenty-four hour ambulatory blood pressure monitoring was performed with an Accutracker 2, Suntech model 104 device (Suntech Medical Instruments, CA, U.S.A.) using the R wave gated auscultatory method. Blood pressure was measured four times every hour during the day (0700h to 2300h) and twice every hour during the night (2300h to 0700h). Eighty readings were attempted during each recording session. The average number of readings acceptable for evaluation were equal in the two groups (87% at the initial investigation and 83% during follow-up). One recording session with more than 20% technical errors was excluded. Recordings were analysed by a personal computer (Accusoft, Suntech Medical Instruments).

### Measurements of skin perfusion responses to acetylcholine and sodium nitroprusside

Determination of endothelium-dependent and -independent vasodilatation in the forearm skin microcirculation was performed by iontophoresis of acetylcholine and sodium nitroprusside combined with laser-Doppler perfusion measurements as previously described<sup>[10,11]</sup>. Microvascular perfusion was measured in arbitrary units (AU) and the stimuli were chosen according to previous studies at our laboratory<sup>[11]</sup>.

All studies were conducted with commercially available equipment (DP1T/7 large area probes, DRT4 Research version 4.24, Moor Instruments Ltd, U.K.). Absolute iontophoresis perfusion responses compared to baseline (baseline perfusion in AU subtracted from the absolute mean perfusion in each period of the protocol) for both acetylcholine and sodium nitroprusside solutions were calculated as the cumulative area under the perfusion vs time curve (AU  $\times$  s).

### Laboratory measurements

Trough levels of cyclosporine were determined 12 h after the last dose of the drug. Serum lipids were measured

after overnight fasting, as previously described<sup>[4]</sup>. The phospholipid acids were quantified by gas chromatography<sup>[12]</sup>. Serum creatinine was measured by routine clinical methods and glomerular filtration rate was calculated according to Cockcroft and Gaults formula  $[\text{glomerular filtration rate} = (140 - \text{age}) \times \text{bodyweight} \times 1.23 / \text{creatinine}]$ . In women, this value was multiplied by 0.85<sup>[13]</sup>.

### Statistics

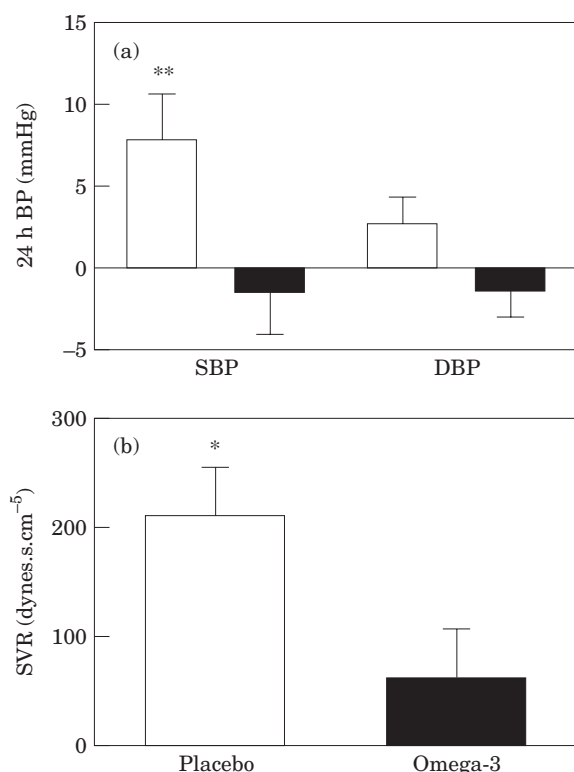
Student's t-test was used for comparison of independent samples and the paired-samples t-test for paired results. Correlations were tested by Pearson's correlation coefficient. Data are given as mean  $\pm$  SEM if not otherwise stated. Probability values are two-sided and considered significant when  $<0.05$ .

### Results

Twenty-one patients in the treatment group and 20 in the placebo group completed the study. Three patients died [two in the placebo group (cerebral infarction and amyotrophic lateral sclerosis) and one in the treatment group (prostate cancer)]. One patient in the treatment group withdrew for personal reasons. The groups were comparable with respect to demographic, clinical and haemodynamic variables (Table 1). In particular, the dose and trough concentrations of cyclosporine were comparable at baseline (Table 1) and at the end of the study. The body mass index remained unchanged in the groups. There was no statistical difference in any parameter measured between patients taking antihypertensive medication or previously untreated (data not shown). None of the patients withdrew from the study because of side effects.

### Blood pressure

With similar 24 h blood pressure measurement at baseline (Table 1), the placebo group demonstrated a significant rise in systolic blood pressure ( $8 \pm 2$  mmHg,  $P=0.01$ ) and an insignificant rise in diastolic blood pressure ( $3 \pm 2$  mmHg;  $P=0.10$ ) accompanied by a significant rise in systemic vascular resistance of 14% ( $P<0.05$ , Fig. 1) after 12 months. In contrast, no changes were observed in these variables in the omega-3 group. In fact, a significant difference was evident between groups analysing changes in systolic blood pressure ( $P=0.02$ ), with a similar trend for changes in diastolic blood pressure ( $P=0.07$ ). Nine patients in the treatment group were normotensive after 12 months, while all patients in the placebo group were still considered hypertensive<sup>[9]</sup> at the end of the study ( $P<0.01$ , between groups).



**Figure 1** Mean changes in (a) 24 h systolic blood pressure (SBP) and diastolic blood pressure (DBP), and (b) systemic vascular resistance (SVR) compared with baseline in heart transplant recipients given placebo (□, n=20) or omega-3 fatty acids (■, n=21) for 12 months (mean  $\pm$  SEM). \*\* $P < 0.01$  vs baseline, \* $P < 0.05$  vs baseline.

In both groups of patients an abnormal circadian blood pressure profile was evident at baseline, with only a modest nocturnal decline in systolic and diastolic blood pressure, respectively  $6 \pm 3\%$  and  $6 \pm 2\%$  (placebo group) and  $5 \pm 2\%$  and  $5 \pm 3\%$  (omega-3 group). At the end of the study, both groups were still 'non-dippers' according to Smyth *et al.*<sup>[14]</sup>, and this lack of nocturnal decline was even more evident after 12 months in the placebo group ( $3 \pm 2\%$  and  $3 \pm 2\%$ ) while increasing in the treatment group ( $8 \pm 2\%$  and  $7 \pm 2\%$ ;  $P = 0.06$  for comparison between groups) (Fig. 2). Thus, omega-3 fatty acids seem to prevent a rise in blood pressure and to some extent improve its diurnal variation. No change in heart rate was observed in the two groups during the study period.

### Serum phospholipids

Serum eicosapentaenoic and docosahexaenoic acid increased significantly over time in the omega-3 group, but not in the placebo group (Table 2). The relationship between changes in 24 h blood pressure and serum phospholipids was studied in the treatment group, and a significant correlation was found between changes in 24 h systolic blood pressure and the combined changes

in eicosapentaenoic and docosahexaenoic acid (Fig. 3). There was also a significant correlation between baseline levels and changes in eicosapentaenoic and docosahexaenoic acid during the study period ( $r = -0.50$ ,  $P = 0.03$ ), suggesting that patients with low initial levels of eicosapentaenoic and docosahexaenoic acid had the greatest increase in these serum phospholipids during the study period.

### Central haemodynamic variables and peripheral vasodilatory capacity

Since previous trials have demonstrated an increase in blood pressure together with an increase in left ventricular volumes during long-term follow-up after heart transplantation<sup>[1]</sup>, we measured left ventricular function, both invasively and non-invasively. During the 12-month follow-up, we found no change in the following variables: left ventricular volumes or mass, indices of systolic and diastolic function as assessed by echocardiography, or left ventricular ejection fraction and end-diastolic pressure as assessed by left-sided heart catheterization in either the placebo or the omega-3 group (Table 3). Moreover, no differences in endothelium-dependent or -independent vasodilation of the skin microcirculation were observed in either group (Table 3).

### Kidney function

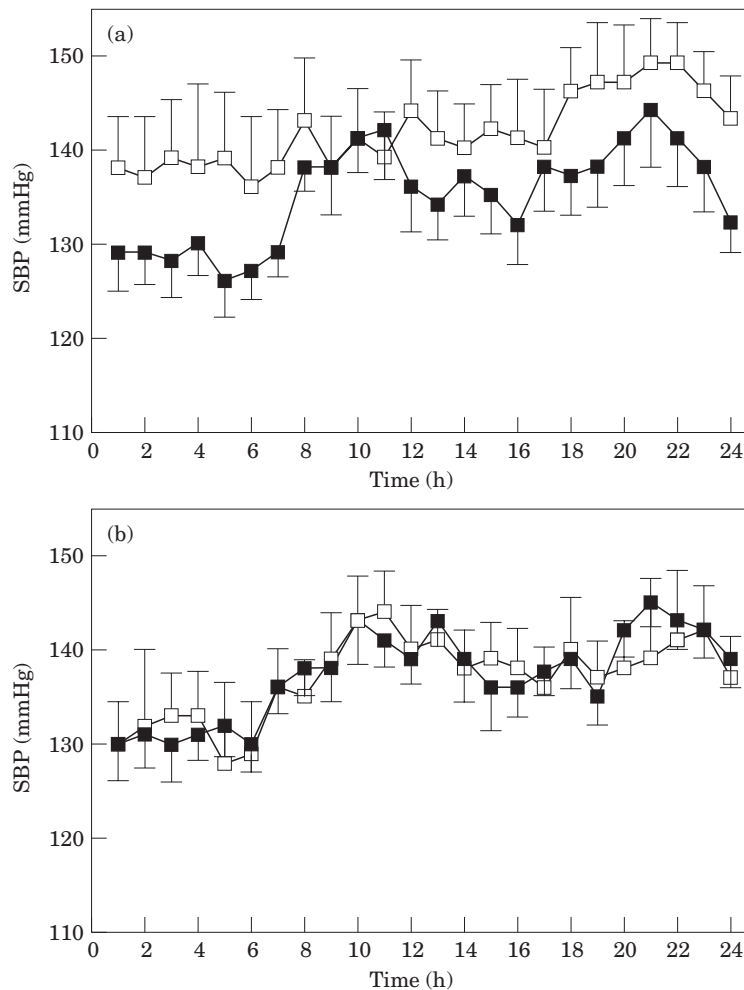
Serum creatinine was not different between the groups at baseline, but increased significantly ( $121 \pm 6$  to  $130 \pm 5$   $\text{mmol} \cdot \text{l}^{-1}$ ,  $P < 0.01$ ) in the placebo group. In contrast, no increase was found in the omega-3 group (Fig. 4). The calculated glomerular filtration rate decreased ( $74 \pm 5$  to  $68 \pm 4$   $\text{ml} \cdot \text{min}^{-1}$ ,  $P = 0.02$ ) in the placebo group, while no change was observed in the omega-3 group (Fig. 4). While a statistical correlation was found between systolic blood pressure and creatinine in all patients at baseline ( $r = 0.38$ ,  $P = 0.01$ ), no such association was evident between changes in creatinine and systolic blood pressure during the study period in either the placebo or the omega-3 groups (data not shown).

### Serum lipids

With similar baseline values (Table 3), omega-3 fatty acids induced a significant decrease in triglyceride levels ( $P < 0.01$ ) and tended to increase HDL-cholesterol levels ( $P = 0.08$ ). No such changes were seen in the placebo group (Table 2).

## Discussion

Arterial hypertension develops in the majority of heart transplant recipients<sup>[1]</sup>. Except for one 4-year longitudinal study observing a continued rise in blood pressure



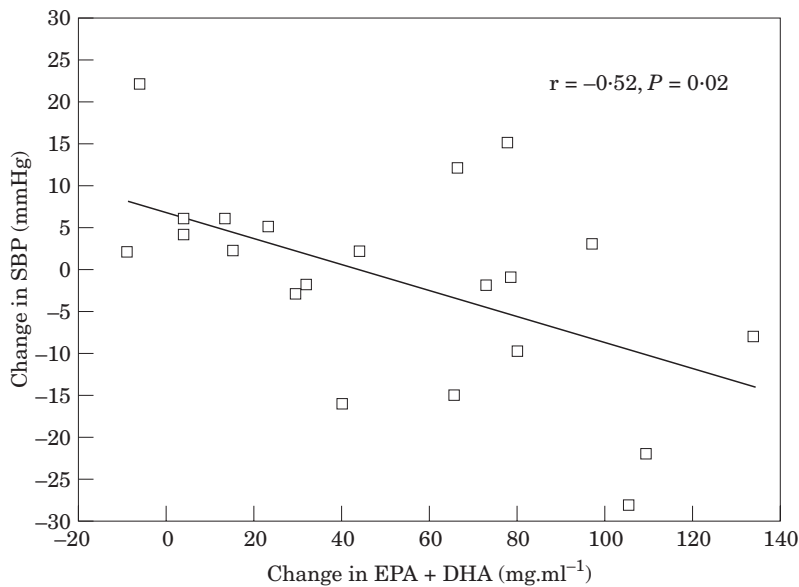
**Figure 2** Twenty-four hour mean systolic blood pressure (SBP) at baseline (■) and after 12 months (□) in the placebo (n=20) (a) and omega-3 fatty acids group (n=21) (b). Each square represents a group mean, with vertical bars indicating SEM.

**Table 2** Serum phospholipid fatty acids and lipids in the omega-3 fatty acids (n=21) and placebo (n=20) group

	Omega-3 fatty acids			Placebo			Differences in changes between groups
	Baseline	12 months	Change	Baseline	12 months	Change	
<b>Lipids</b>							
Triglycerides (mmol . l <sup>-1</sup> )	2.2 ± 0.3	1.7 ± 0.2	-0.6 (-0.9, -0.2)**	1.9 ± 0.3	2.0 ± 0.3	0.1 (-0.3, 0.6)	0.07
Total cholesterol (mmol . l <sup>-1</sup> )	6.9 ± 0.3	6.8 ± 0.3	-0.1 (-0.42, 0.3)	6.2 ± 0.2	6.1 ± 0.2	-0.1 (-0.3, 0.2)	0.50
HDL cholesterol (mmol . l <sup>-1</sup> )	1.3 ± 0.1	1.5 ± 0.1	0.2 (-0.02, 0.3)	1.4 ± 0.1	1.4 ± 0.1	0 (-0.1, 0.2)	0.38
LDL cholesterol (mmol . l <sup>-1</sup> )	4.4 ± 0.1	4.4 ± 0.1	0.0 (-0.5, 0.6)	3.9 ± 0.1	3.9 ± 0.1	0 (-0.5, 0.5)	0.57
<b>Phospholipid fatty acids</b>							
EPA (mg . l <sup>-1</sup> )	52 ± 7	92 ± 7	39 (27, 51)***	46 ± 10	44 ± 8	-2 (-13, 9)	<0.001
DHA (mg . l <sup>-1</sup> )	118 ± 7	134 ± 6	15.2 (4, 28)*	118 ± 9	112 ± 9	-6 (-22, 11)	0.04

Data are given as mean ± SEM at baseline and 12 months. Changes are given as mean, and 95% CI in parenthesis. \**P*<0.05, \*\**P*<0.001, \*\*\**P*<0.001 vs baseline.

EPA=eicosapentanoic acid; DHA=docosahexanoic acid.



**Figure 3** Relationship between changes in systolic blood pressure (SBP) and serum eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) in 21 heart transplant recipients during 12 months treatment with omega-3 fatty acids.

over time<sup>[15]</sup>, most studies, among them our own<sup>[4,5]</sup>, have been limited to the first post-transplant year. The present study extends these findings demonstrating that blood pressure and particularly systolic blood pressure, may continue to rise for years after heart transplantation, even when cyclosporine and prednisolone are kept at constant low levels. Arterial stiffening with age is acknowledged as the main cause of isolated systolic hypertension in the non-transplant elderly population<sup>[16]</sup>. Structural changes of the vascular wall are described in patients with heart failure and do not completely normalize 1 year after transplantation<sup>[17]</sup>. Increased peripheral vascular tone over time might lead to further vascular morphological changes and stiffness of the arterial wall, making systolic rather than diastolic hypertension more prominent late after heart transplantation.

The efficacy of omega-3 fatty acid supplements in reducing blood pressure may vary in different patient populations and biochemical subgroups<sup>[18]</sup>. As previously shown<sup>[4,19]</sup>, the greatest decrease in blood pressure occurred in patients with the greatest increase in plasma eicosapentaenoic and docosahexaenoic acid. Furthermore, we found a negative correlation between baseline levels and an increase in eicosapentaenoic and docosahexaenoic acid. This may indicate that an initially high acceptor-pool for polyunsaturated fatty acids, possibly due to low intake of fatty fish, is important for the incorporation of eicosapentaenoic and docosahexaenoic acid in biomembranes, favouring antihypertensive effects of omega-3 fatty acids<sup>[19,20]</sup>.

The present study supports recent observations that heart transplant recipients have a subnormal nocturnal decline in blood pressure<sup>[21]</sup> and demonstrates improved

diurnal blood pressure variation following supplementation of omega-3 fatty acids. Lack of diurnal variability of blood pressure and heart rate have been associated with increased risk of cardiovascular events in non-transplant patients<sup>[22]</sup>, but remain to be studied in heart transplant recipients. While previous studies in non-transplant subjects have observed a heart rate reducing effect of omega-3 fatty acids<sup>[23]</sup>, no change in 24 h mean heart rate or nocturnal heart rate reduction were observed in either group in the present study.

An important finding in the present study was that the rise in blood pressure and systemic vascular resistance was not associated with changes in resting haemodynamics or development of left ventricular hypertrophy. However, the blood pressure increase was limited and at baseline most patients were already receiving calcium channel blockers and/or angiotensin-converting enzyme inhibitors that are known to regress left ventricular hypertrophy, possibly counteracting a potential increase in left ventricular mass in the placebo group. Also, the time-span may have been too short for the development of significant changes.

The present study also demonstrates a favourable effect of omega-3 fatty acids on renal function in heart transplant recipients. These results agree with previous findings in patients with renal transplants and cyclosporine treated psoriasis<sup>[7,8,24,25]</sup>. Moreover, the beneficial effect on renal function partly depended on an increase in eicosapentaenoic and docosahexaenoic acid. The mechanism involved is unknown, but experimental studies have shown that omega-3 fatty acids may increase thromboxane A<sub>3</sub> formation, coinciding with a fall in thromboxane A<sub>2</sub> and a significant increase in total prostacyclin levels<sup>[26]</sup>. This potentially vasodilatory

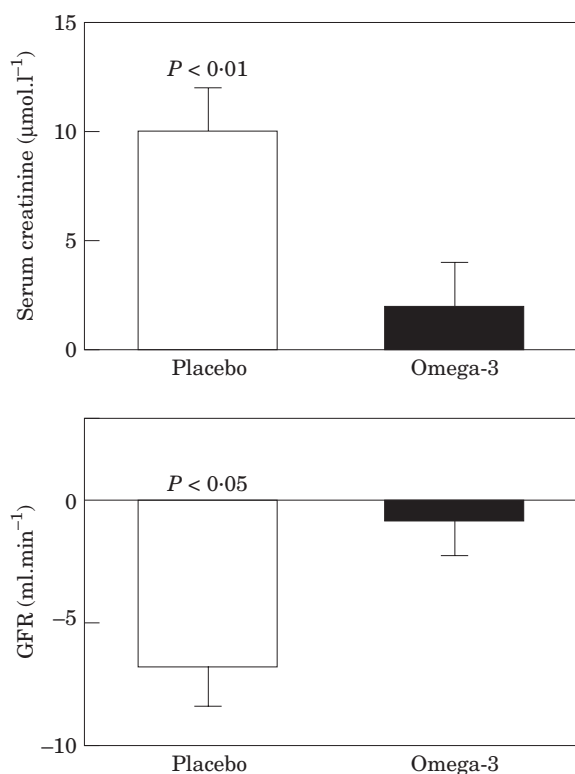
Table 3 Resting haemodynamics, echocardiographic and microvascular parameters before and after 12 months of medication

	Omega-fatty acids			Placebo			Differences in changes between groups
	Baseline	12 months	Change	Baseline	12 months	Change	
<b>Haemodynamics</b>							
SVR (dynes $\cdot$ s $^{-1}$ $\cdot$ cm $^{-5}$ )	1634 $\pm$ 63	1699 $\pm$ 72	64 (-111, 241)	1582 $\pm$ 64	1794 $\pm$ 62	211 (73, 249)*	0.180
LVEF (%)	70 $\pm$ 5	68 $\pm$ 3	- (-13, 9)	72 $\pm$ 4	70 $\pm$ 2	-2 (-13, 9)	0.986
LVEDP (mmHg)	10.6 $\pm$ 0.4	12.2 $\pm$ 1.4	1.6 (-1.7, 4.7)	9.5 $\pm$ 1.0	12.6 $\pm$ 1.4	3 (-0.3, 6.0)	0.155
MAP (mmHg)	16 $\pm$ 1	15 $\pm$ 1	-1 (-2, 1)	16 $\pm$ 2	17 $\pm$ 2	1 (-2, 5)	0.933
PCW (mmHg)	7.6 $\pm$ 0.6	6.8 $\pm$ 0.5	-0.8 (-2.2, 0.8)	7.8 $\pm$ 0.9	8.1 $\pm$ 0.7	0.3 (-1.0, 1.5)	0.581
CI (l $\cdot$ min $^{-1}$ $\cdot$ m $^{-2}$ )	3.0 $\pm$ 0.3	2.3 $\pm$ 0.2	-0.7 (-1.2, 0.1)	3.2 $\pm$ 0.2	2.6 $\pm$ 0.1	-0.6 (-1.1, 0.2)	0.733
<b>Echocardiography</b>							
LVEDD (cm)	4.8 $\pm$ 0.1	4.9 $\pm$ 0.2	0.1 (-0.1, 0.2)	4.8 $\pm$ 0.2	4.8 $\pm$ 0.1	0.1 (-0.2, 0.4)	0.344
FS (%)	30 $\pm$ 2	33 $\pm$ 1	3 (-1, 6)	33 $\pm$ 1	33 $\pm$ 1	0 (-3, 4)	0.435
Septal thickness (cm)	1.23 $\pm$ 0.05	1.20 $\pm$ 0.03	-0.03 (-0.1, 0.1)	1.15 $\pm$ 0.04	1.16 $\pm$ 0.04	0.01 (-0.05, 0.08)	0.324
Posterior wall (cm)	1.13 $\pm$ 0.05	1.12 $\pm$ 0.05	-0.02 (-0.1, 0.06)	1.10 $\pm$ 0.05	1.09 $\pm$ 0.04	-0.02 (-0.11, 0.06)	0.993
E/A ratio	1.9 $\pm$ 0.2	1.8 $\pm$ 0.3	-0.1 (-0.4, 0.6)	1.6 $\pm$ 0.2	1.8 $\pm$ 0.2	0.2 (-0.1, 0.6)	0.284
Deceleration time (ms)	173 $\pm$ 12	170 $\pm$ 15	-3 (-49, 44)	177 $\pm$ 12	187 $\pm$ 14	10 (-9, 10)	0.581
<b>Endothelium-dependent and -independent vasodilation</b>							
Ach response (AU $\times$ s)	754 132 $\pm$ 125 193	698 626 $\pm$ 153 931	-55 506 (39 364, -99 375)	639 717 $\pm$ 140 810	600 527 $\pm$ 135 421	-39 190 (-71 992, 25 037)	0.243
Nitrid response (AU $\times$ s)	895 470 $\pm$ 163 403	762 400 $\pm$ 19 165	-13 372 (26 562, -32 451)	924 417 $\pm$ 168 059	828 578 $\pm$ 144 691	-96 559 (-12 742, 33 430)	0.533

Data are given as mean  $\pm$  SEM at baseline and 12 months. Changes are given as mean, and 95% CI in parenthesis.

\*  $P < 0.05$ .

SVR = total peripheral resistance; LVEF = left ventricular ejection fraction; LVEDP = left ventricular end diastolic pressure; MAP = mean pulmonary artery pressure; PCW = pulmonary capillary wedge pressure; CI = cardiac index; LVEDD = left ventricular end diastolic dimension; FS = fractional shortening; Ach = acetylcholine.



**Figure 4** Mean changes in serum creatinine (a) and glomerular filtration rate (GFR) (b) (mean  $\pm$  SEM) compared to baseline in heart transplant recipients receiving placebo (n=20) or omega-3 fatty acids (n=21) for 12 months. \* $P < 0.05$ , \*\* $P < 0.01$  vs baseline.

effect of omega-3 fatty acids may therefore promote improved renal function and blood pressure control. While a modest relationship between creatinine and blood pressure was evident at baseline, no direct relationship was found between the rise in blood pressure and the decline in renal function, as assessed by serum creatinine and calculated glomerular filtration rate. Nevertheless, although our findings may suggest that the hypertension after heart transplantation is not a direct consequence of cyclosporine-induced nephrotoxicity, renal impairment is suggested to play a pathogenic role<sup>[1,2]</sup>, and it is tempting to hypothesize that the beneficial effect of omega-3 fatty acids on kidney function may at least partly contribute to its antihypertensive effect.

Altered renal haemodynamics alone probably do not explain the increased systemic vascular resistance in heart transplant recipients<sup>[1]</sup>, and our previous findings of impaired skin microvascular endothelium-dependent vasodilatory capacity in these patients<sup>[27]</sup> suggest that other vascular beds are also involved. Furthermore, we have shown beneficial effects on peripheral vascular reactivity in the skin microcirculation by omega-3 fatty acids early after heart transplantation<sup>[4]</sup> and others have observed increased responses to acetylcholine after supplementation with omega-3 fatty acids in patients with non-insulin-dependent diabetes<sup>[28]</sup>. The present study

showed no effect, however, on endothelium-dependent or -independent vasodilation in the skin microcirculation long-term after transplantation. Differences in study population and methods used to evaluate peripheral vasomotor function may explain these diverging findings. Also, an effect of omega-3 fatty acids on renal or larger resistance vessels could still be possible since the microcirculation in the skin and skeletal muscle appears to be differentially regulated<sup>[29,30]</sup>.

Lipid and lipoprotein abnormalities are frequently found after heart transplantation, and higher concentrations of both serum cholesterol and particularly triglycerides are associated with an increased risk of graft coronary artery disease<sup>[31,32]</sup>. Our findings of an improved serum lipoprotein profile with omega-3 fatty acids are supported by previous findings in non-transplant patients<sup>[33,34]</sup>. Treatment with omega-3 fatty acids may therefore have multiple clinically important and possibly synergistic effects, not only improving blood pressure control and renal function, but also lowering serum triglycerides.

### Conclusion

The present study demonstrates that treatment with omega-3 fatty acids may inhibit the long-term continuous rise in blood pressure after heart transplantation. The beneficial effect of omega-3 fatty acids is dependent on an increase in serum eicosapentaenoic and docosahexaenoic acid. Furthermore, omega-3 fatty acids appear to offer a renal protective effect and reduce serum levels of triglycerides, making it a potentially attractive agent in the treatment of post-transplant hypertension.

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