The n–3 fatty acids eicosapentaenoic acid and docosahexaenoic acid increase systemic arterial compliance in humans1–3

Paul Nestel, Hideki Shige, Sylvia Pomeroy, Marja Cehun, Mavis Abbey, and Daniel Raederstorff

ABSTRACT
Background: n–3 Fatty acids influence vascular function, but the effect of individual fatty acids on systemic arterial compliance (SAC) has not been reported. SAC, which reflects arterial elasticity, is emerging as a new cardiovascular risk factor and appears to predict future cardiovascular events.

Objective: We tested whether the n–3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) improve SAC in dyslipidemic subjects.

Design: Thirty-eight dyslipidemic subjects were randomly assigned to receive 3 g EPA/d (n = 12), 3 g DHA/d (n = 12), or a placebo (n = 14) in a 7-wk parallel, double-blind trial. Arterial functions were measured at the beginning and end of the interventions. Plasma lipids and plasma fatty acids were also measured.

Results: Consumption of the n–3 fatty acids significantly increased SAC, whereas consumption of the placebo did not (P = 0.043; repeated-measures analysis of variance across the 3 groups); the increase was 36% with EPA and 27% with DHA. The major components contributing to the increase in SAC (systolic and pulse pressures and total vascular resistance) tended to decrease but not significantly. Plasma total and VLDL triacylglycerol were significantly lower in the n–3 fatty acid groups (P = 0.026 and 0.006, respectively; repeated-measures analysis of variance) than in the placebo group.

Conclusion: EPA and DHA increase SAC and tend to reduce pulse pressure and total vascular resistance, effects that may reduce the risk of adverse cardiovascular events. Am J Clin Nutr 2002;76:326–30.

KEY WORDS Systemic arterial compliance, n–3 fatty acids, plasma lipids, arterial pressure, cardiovascular disease, eicosapentaenoic acid, docosahexaenoic acid

INTRODUCTION
Investigators studying n–3 fatty acids have concluded that substantial epidemiologic and other evidence shows that eating fish may benefit people at high risk for ischemic heart disease (IHD; 1). A GISSI long-term randomized controlled trial with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) showed significant reductions in IHD events (2). A previous secondary prevention trial in which modest amounts of n–3 fatty acids were consumed suggested that sudden cardiac deaths were reduced (3).

A range of known and potential mechanisms have been reported that may account for less IHD and atherosclerosis in response to long-chain n–3 fatty acids (4). Sudden cardiac deaths occurred less frequently in individuals who habitually ate fish (5), which was consistent with the antiarrhythmic properties of n–3 polyunsaturated acids (6). Antihypertensive effects were documented in subjects with raised blood pressure (7), and this effect was shown to be most likely attributable to DHA (8). Vascular functions are also influenced by n–3 polyunsaturated acids. Fish oil supplementation affects endothelial function. Goodfellow et al (9) reported improved flow-mediated dilation of the brachial artery, and we (10) and others (11) showed improved, nitric oxide–mediated vasodilatation in the microcirculation of the forearm. Increased distensibility or compliance within large arteries was reported in diabetics consuming fish oil (12). We observed significant improvement in systemic arterial compliance (SAC) in dyslipidemic subjects with consumption of α-linolenic acid (plant n–3 fatty acid; 13). Reduced compliance or increased stiffness in the large arterial circulation is regarded as a major factor in the development of systolic hypertension and increased pulse pressure, contributing to increased left ventricular load and to diminished coronary flow during diastole (14). Because of increasing evidence linking heightened pulse pressure, a reflection of increased arterial stiffness, to increased coronary risk (15, 16), interventions that improve arterial compliance are thought likely to reduce risk for IHD.

Because the relative benefits of each of the major long-chain n–3 fatty acids are largely unknown, we investigated the effects of relatively purified EPA and DHA on SAC in dyslipidemic subjects.

SUBJECTS AND METHODS

Experimental design
The investigation had a double-blind parallel design, comprising 3 groups: 1 group consumed placebo capsules and the other 2 consumed either EPA- or DHA-containing capsules. The study

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began with a 2-wk familiarization period during which the subjects were instructed about background diet, other medications, physical activity, and alcohol intake (when relevant) and acquainted with the procedures, including measurement of arterial compliance. They were then assigned to 1 of the 3 groups from predetermined random numbers. The intervention phase lasted 7 wk.

SAC was measured in the morning at the beginning and end of the 7-wk intervention phase. Blood was collected at the beginning and end, after the subjects had fasted overnight, to measure plasma lipids, lipoproteins, and fatty acid profiles.

Test subjects

Forty-one men and women were recruited who met the inclusion criteria, which included age 40–69 y, postmenopausal if female, body mass index (in kg/m²) preferably between 25 and 29, and one or more of the following: plasma total cholesterol > 5.5 mmol/L, triacylglycerol > 2 mmol/L, HDL cholesterol < 1.0 (men) or 1.2 (women) mmol/L. Exclusion criteria included smoking; alcohol consumption of > 4 standard drinks/d; refusal to suspend hormone replacement therapy (women), vitamin and other supplements, or antilipidemic or antihypertensive therapy; refusal to comply with certain dietary requirements (avoiding fish and plant n–3 fatty acid foods); and metabolic disorders such as diabetes. When relevant, consumption of the excluded medications was stopped 6 wk before the study to remove the exclusion barrier.

Two subjects withdrew because of work pressures and one was withdrawn because of excess alcohol consumption. Of the 38 subjects who completed the study, 12 had been consuming EPA, 12 DHA, and 14 the placebo. The study was approved by the Ethics Committee on Human Experimentation of the Alfred Group of Hospitals, and volunteers were fully informed before written consent was requested and obtained.

Investigational products

The test material was prepared in the laboratories of F Hoffmann-La Roche (Basel, Switzerland) and encapsulated by RP Scherer GmbH & Co KG (Eberbach-Baden, Germany). Each subject consumed four 1-g capsules/d. The placebo was olive oil (70% oleic, 10% palmitic, and 11% linoleic acid by weight). The n–3 fatty acids were prepared as ethyl esters, and the capsules contained ascorbyl palmitate and all-rac-α-tocopherol as antioxidants. The EPA supplement comprised 85% total fatty acids, to which EPA contributed 76%, DHA 1.7%, and eicosatetraenoic (20:4n–3) acid 3.1%. The DHA capsules comprised 70.7% DHA, 4.1% EPA, and 13.2% docosapentaenoic (22:5n–3) acid (DPA). Thus, the 4 capsules provided either 2.8 g oleic acid or 3.04 g EPA or 2.84 g DHA plus 0.52 g DPA.

Measurements

Systemic arterial compliance

Noninvasive methods such as those used here to obtain hemodynamic data, including the viscoelastic properties of arterial compliance, have been validated by Marcus et al (17) by comparing directly the intraaortic pressure with indirectly measured subclavian artery pressure.

SAC was estimated with the area method of Liu et al (18), which requires measurement of aortic blood flow and associated driving pressure to derive an estimated compliance over the total arterial system with the formula

\[
SAC = \frac{Ad}{[R(Ps - Pd)]}
\]

where \(Ad\) is the area under the blood pressure diastolic decay curve from end systole to end diastole, \(R\) is the total peripheral resistance, \(Ps\) is the end-systolic blood pressure, and \(Pd\) is the end-diastolic blood pressure. Aortic flow was measured from a 4-MHz continuous wave Doppler flow velocimeter (Multidopex MDI; Huntley Technology, Cardiff, United Kingdom) and pressure by applanation tonometry of the right carotid artery (Millar Mikrotip pressure transducer; Millar Instruments, Houston). Pressures were calibrated against Dinamap brachial artery pressure (CRITIKON 1846 SX; North Ryde, Australia). Blood pressures were measured automatically at frequent intervals during the measurement of SAC. The methodology has been described fully by Cameron and Dart (19), whose purpose-written software was used to analyze data. For each measurement of SAC, 3 sets of sequential measurements were made, each comprising ≥ 10 satisfactory pressure-flow waves. At least 2 of the 3 values for SAC had to meet a predetermined low SE for acceptance and were averaged. The software program also provided values for pulse pressure and total vascular resistance, which are integral to the derivation of SAC.

**Plasma lipids**

Plasma was separated from chilled blood samples and frozen at −80 °C. Measurements were carried out in batches for plasma total cholesterol, triacylglycerol, and HDL cholesterol after precipitating apolipoprotein B–containing lipoproteins in a Cobas-Bio automated analyzer (Roche Diagnostica, Basel, Switzerland). Triacylglycerol concentrations in VLDL were measured after those lipoproteins were separated by ultracentrifugation at 106 × g for a minimum of 8 h at 4°C in an SW41 Ti rotor with the use of a bench-top ultracentrifuge (Beckman Industries, Palo Alto, CA). Fatty acids from whole plasma were analyzed as the methyl esters by gas-liquid chromatography and expressed as percentages; values < 1% have been excluded from statistical evaluation except for docosapentaenoic acid, which contributed 400 mg/d during the DHA test phase.

**Statistical analysis**

The results were analyzed by repeated-measures analysis of variance (RM-ANOVA). The group × time (before and after intervention) interaction was used to test the global hypothesis that the changes in the levels of the variables over the period of treatment were parallel for the 3 treatments. For each variable an analysis of residuals was performed. In the case of TVR (total vascular resistance), there was a marked increase in scatter pari passu with the estimate, which was completely corrected by log transformation. The main hypothesis was that SAC is improved (increased) with EPA and DHA. Correlations were explored by the Pearson product-moment correlation coefficient (\(r\)), with the use of a two-tailed test for significance. The analyses were performed with SYSTAT 9.01 (SPSS Inc, Chicago). Two-sided values of \(P < 0.05\) were regarded as indicating statistically significant differences.

**RESULTS**

Body weights increased on average by 1 kg in the 2 n–3 fatty acid groups, but this increase was not significant (Table 1). Daily food diaries compiled by the subjects showed that they had avoided fish and fish products and foods rich in α-linolenic acid.
TABLE 1
Characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo group (n = 9 M, 5 F)</th>
<th>EPA group (n = 5 M, 7 F)</th>
<th>DHA group (n = 7 M, 5 F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61 ± 9</td>
<td>57 ± 7</td>
<td>55 ± 6</td>
</tr>
<tr>
<td>Weight at baseline (kg)</td>
<td>80 ± 14</td>
<td>80 ± 9</td>
<td>77 ± 10</td>
</tr>
<tr>
<td>Weight at end (kg)</td>
<td>80 ± 14</td>
<td>81 ± 9</td>
<td>78 ± 10</td>
</tr>
</tbody>
</table>

\(^{1}\) SD. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid. None of the variables differed significantly between the 3 groups.

Plasma lipids

The initial values of average plasma lipids for the 3 groups were not significantly different for corresponding lipids. Plasma total cholesterol and LDL cholesterol did not change significantly over time with either treatment or placebo.

Both plasma total triacylglycerol and VLDL triacylglycerol concentrations fell significantly over the 7-wk intervention in each of the n−3 fatty acid groups, as shown in Table 2 (P = 0.026 for triacylglycerol and P = 0.006 for VLDL triacylglycerol, RM-ANOVA with Bonferroni correction). The reductions in triacylglycerol values were not significantly different between the EPA and DHA groups. HDL cholesterol rose in all 3 groups, and the increments did not differ among the groups (Table 2).

Systemic arterial compliance and arterial pressure

The baseline SAC values for the 3 groups did not differ significantly (ANOVA; Table 3). The values for the placebo group remained unchanged [0.150 ± 0.08 units (\(\pm \) SD; units are dimensionally equal to mL/mm Hg) between baseline and the end of the 7-wk intervention]. In contrast, SAC increased significantly with each n−3 fatty acid. For the EPA group, SAC rose 36%, from 0.149 ± 0.06 to 0.203 ± 0.06 units; for the DHA group the baseline and final values were 0.147 ± 0.05 and 0.187 ± 0.07 units, a rise of 27%. The changes in SAC across the 3 groups were significant (P = 0.043; RM-ANOVA). ANOVA with group \(\times\) time interaction for SAC as dependent variable provided the following P values: across all 3 groups, P = 0.043; for placebo compared with EPA, P = 0.028 (with Dunnett’s correction, P = <0.05); for placebo compared with DHA, P = 0.091; for EPA compared with DHA, P = 0.45.

Thus, EPA may have contributed more significantly than did DHA to the effect across the 3 groups, but inspection of the raw data (Table 3) suggests that the inequality revealed by the RM-ANOVA was between the placebo on the one hand and the treatment with EPA and DHA on the other. Subset analysis failed to distinguish between the effects of EPA and DHA (P = 0.46). Therefore the n−3 group data were pooled as a single active treatment group and compared with the data from the placebo group. The outcome was P = 0.015 (with Dunnett’s correction, P < 0.05), reinforcing the inference that EPA and DHA had an effect on SAC whereas the placebo did not.

Heart rates did not change significantly (Table 3). Systolic and diastolic pressures were measured automatically during calculation of SAC (Table 3). Neither diastolic nor mean pressures changed significantly in any of the 3 treatment groups. Although there was a trend for systolic and pulse pressures and TVR to fall as SAC rose, these changes were not statistically significant.

Plasma fatty acids

There were minor insignificant changes from baseline to the end of treatment in the profile of fatty acids in the placebo group. In the EPA group, mean (±SD) EPA rose from 1.6 ± 0.9% of total fatty acids to 9 ± 1.8% (P < 0.001). This did not translate into an increase in DHA. DPA, the intermediate fatty acid, increased ∼3-fold, from 0.7 ± 0.1% to 1.9 ± 0.3% (P < 0.001). By contrast, there was no increase in plasma DPA in the DHA group, even though DPA composed 13% of the supplement’s fatty acids. In the DHA group, plasma DHA rose from 2.2 ± 0.6% to 7.2 ± 1.4% (P < 0.001). Plasma EPA, present in minor amounts in the supplement, also increased significantly, from 1.1 ± 0.3% to 2.7 ± 1.1% (P < 0.01).

Correlations

LogSAC was inversely correlated with systolic pressure (r = −0.55), pulse pressure (r = −0.58), and logTVR (r = −0.50), each being significant (P < 0.001). Plasma EPA was negatively correlated with both triacylglycerol and VLDL triacylglycerol concentrations at the end of the intervention with EPA (r = −0.61, P = 0.036 and r = −0.71, P = 0.01, respectively) and positively with the HDL cholesterol concentration (r = 0.61, P = 0.036). Plasma DHA was significantly correlated with plasma triacylglycerol (r = −0.66, P = 0.018) and tended to be directly correlated with HDL cholesterol.

Because both total triacylglycerol and VLDL triacylglycerol concentrations changed significantly with treatment, a possible association between these lipids and SAC was explored. VLDL triacylglycerol appears to have been a weak but significant linear predictor of logSAC (n = 76; r = −0.243, P = 0.035).

TABLE 2
Plasma lipid and lipoprotein concentrations at baseline and after 7 wk of intervention

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo group (n = 14)</th>
<th>EPA group (n = 12)</th>
<th>DHA group (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 7</td>
<td>Baseline</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.61 ± 1.03(^{2})</td>
<td>6.82 ± 1.07</td>
<td>6.55 ± 1.21</td>
</tr>
<tr>
<td>HDL</td>
<td>1.29 ± 0.44</td>
<td>1.38 ± 0.41</td>
<td>1.27 ± 1.33</td>
</tr>
<tr>
<td>LDL</td>
<td>4.54 ± 1.0</td>
<td>4.67 ± 1.0</td>
<td>4.56 ± 1.13</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.51 ± 0.79</td>
<td>1.69 ± 0.74</td>
<td>1.57 ± 0.8</td>
</tr>
<tr>
<td>VLDL(^{3})</td>
<td>0.87 ± 0.64</td>
<td>0.98 ± 0.63</td>
<td>0.87 ± 0.54</td>
</tr>
</tbody>
</table>

\(^{1}\) EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid. P values are raw, unadjusted values attached to group \(\times\) time (interaction in repeated-measures ANOVA across all 3 groups).

\(^{2}\) ± SD.

\(^{3}\) Significant effect of time (repeated-measures ANOVA with Bonferroni correction): \(^{4}\) P = 0.026, \(^{4}\) P = 0.006.
DISCUSSION

Systemic arterial compliance

The major finding of this study was the improvement in SAC with n−3 fatty acid supplementation. The increases in SAC over the 7-wk treatment were 36% with EPA and 27% with DHA. Using the present methodology, we previously showed a significant increase in SAC when similar subjects consumed 20 g α-linolenic acid/d (13). Arterial compliance improves in diabetics treated with fish oil (12). To date, the present study appears to be the only evaluation of EPA and DHA on large elastic artery function.

There have been measures of other parameters of vascular function in groups of individuals consuming either fish oil, individual n−3 fatty acids, or fish. Chin et al (10) and Tagawa et al (11) showed that EPA-DHA or EPA alone suppressed the vasoconstrictive effect of norepinephrine or increased vasodilatory responses to acetylcholine in the forearm microcirculation. Goodfellow et al reported improved flow-mediated dilation (9), and Fleischhauer et al (20) reported enhanced vasodilatory response to acetylcholine infused into the coronary circulation of heart transplant patients given fish oil. Left ventricular diastolic filling, an important index of cardiac function, has been shown by Grinsggaard et al (21) to improve in subjects taking DHA and EPA, which might have reflected increased arterial compliance (14).

Arterial pressure

The increase in SAC resulted in part from a trend toward falls in systolic and pulse pressures and in total vascular resistance that was not statistically significant. An improvement in SAC generally reflects a fall either in pressure, more commonly pulse pressure, or in resistance, or, as in the present case, probably both. In the present study this was confirmed with the highly significant inverse correlations between logSAC on the one hand and systolic pressure, pulse pressure, and logTVR on the other. Arterial pressures have been reported in some studies but not in others to have fallen in people eating fish oil or fish (22). A recent study that compared the effects of EPA and DHA on blood pressure concluded that DHA was the active component in fish oil (8). Heart rate variability, another cardiovascular parameter that reflects autonomic function, is influenced beneficially by fish oil (23).

Mechanisms and clinical implications of the changes in SAC

The mechanisms responsible for the improvement in SAC are likely to be multiple. The factors involved in the biomechanics of large elastic and muscular arteries are not as clear as for smaller muscular arteries and the microcirculation, where endothelium-derived vasodilatory nitric oxide predominates. Smooth muscle in the microcirculation is also responsive to sympathetic neuronal activity that has been reported to be modifiable in subjects treated with fish oil (24). Vasoactive eicosanoids that influence aortic hemodynamics respond by changing the balance to less constrictive prostanoids in animals fed fish oil (25). The elastic and collagenous structural components in the aorta are likely to respond also to changes in fluidity induced by highly polyunsaturated fatty acids. It is likely that SAC is influenced by each of the above factors: endothelial function, the tonicity of the smooth muscle coat, and the physical properties of the proteoglycans that have a major role in determining the tensile and viscoelastic properties of extracellular matrix.

The clinical importance of the improved SAC seen with consumption of EPA and DHA lies in the relation between diminishing SAC and increasing cardiovascular risk from hypertension and diabetes (26, 27). The significant inverse—albeit weak—correlation between VLDL triacylglycerol concentration and SAC may be further evidence of the detrimental effect of remnants of triacylglycerol metabolism on arterial compliance. We recently showed such adverse effects on SAC during 6 h of postprandial lipemia (28). Recent studies strongly suggest that diminished arterial compliance, often manifested as increased pulse pressure, predicts adverse cardiovascular events (15, 16). The first substantive intervention trial of patients with IHD treated with ≈1 g/d EPA-DHA showed a significant reduction in major cardiovascular events (2).

Plasma lipids

Whereas many studies of fish oils and of fish have consistently shown reductions in plasma triacylglycerol and more often than not increases in HDL cholesterol (5, 29), little is known about the comparative effects of EPA and DHA. EPA ethyl esters were shown to lower triacylglycerol, although the effect on HDL cholesterol is equivocal (29, 30). We found substantial triacylglycerol lowering with both fatty acids; furthermore, the percentage concentrations of both EPA and DHA in plasma at the end of the interventions correlated significantly and inversely with the plasma triacylglycerol levels at the time (R = −0.65 and −0.63, respectively). HDL cholesterol tended to increase with both EPA and DHA but also rose in the placebo group, so that no significant group difference was found. The mechanisms involved in the

TABLE 3

Systemic arterial compliance (SAC), heart rate, arterial pressures, and total vascular resistance (TVR) at baseline and after 7 wk of intervention†

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n = 14)</th>
<th>EPA group (n = 12)</th>
<th>DHA group (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 7</td>
<td>Baseline</td>
<td>Week 7</td>
</tr>
<tr>
<td>SAC (units)</td>
<td>0.150 ± 0.08±</td>
<td>0.150 ± 0.08±</td>
<td>0.149 ± 0.06</td>
<td>0.203 ± 0.06∥</td>
</tr>
<tr>
<td>Heart rate (min)</td>
<td>64 ± 8</td>
<td>65 ± 8</td>
<td>58 ± 8</td>
<td>60 ± 6</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>132 ± 27</td>
<td>130 ± 19</td>
<td>126 ± 19</td>
<td>121 ± 21</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77 ± 14</td>
<td>77 ± 9</td>
<td>74 ± 8</td>
<td>72 ± 6</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55 ± 19</td>
<td>53 ± 16</td>
<td>51 ± 14</td>
<td>49 ± 16</td>
<td>52 ± 16</td>
</tr>
<tr>
<td>TVR (units)</td>
<td>18.9 ± 9.8</td>
<td>18.3 ± 8.4</td>
<td>16.8 ± 4.2</td>
<td>13.2 ± 4.3</td>
</tr>
</tbody>
</table>

†EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid. P values are raw, unadjusted values attached to group × time (interaction in repeated-measures ANOVA across all 3 groups).

∥0 ± SD.

‡P = 0.028 compared with placebo by analysis of covariance P < 0.05 with Dunnett’s correction.

§P = 0.091 compared with placebo by analysis of covariance with Dunnett’s correction, and not significantly different from EPA (P = 0.45).
lipoprotein and lipid changes in response to n−3 fatty acids have been reviewed recently (4).

The changes in plasma fatty acids (full analysis not shown) included elongation of EPA to DPA with the EPA supplement and an increase in plasma EPA with the DHA supplement, reflecting in part retroconversion of DHA (31).

With the recent availability of increasingly purified long-chain n−3 polyunsaturated fatty acids, the important scientific and clinical questions about the relative benefits of EPA and DHA should become clearer. The present study is the first to report that relatively pure n−3 fatty acids increased SAC in dyslipidemic individuals. Both fatty acids lowered plasma total and VLDL triacylglycerol concentrations.

We gratefully acknowledge the advice of Debbie Hilton and John Ludbrook (Director, Biomedical Statistical Consulting Service, Melbourne) on the statistical analyses of the data.

REFERENCES