Differential Effects of Eicosapentaenoic Acid and Docosahexaenoic Acid on Vascular Reactivity of the Forearm Microcirculation in Hyperlipidemic, Overweight Men

Trevor A. Mori, PhD; Gerald F. Watts, PhD, MD; Valerie Burke, MD; Elisabet Hilme, MD; Ian B. Puddey, MD; Lawrence J. Beilin, MD

Background—Recent evidence supports differential effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the 2 major ω3 fatty acids of marine origin, on blood pressure in humans and vascular reactivity in adult spontaneously hypertensive rats. We investigated possible differences in the effects of purified EPA or DHA on forearm vascular reactivity in overweight hyperlipidemic men that might contribute to the blood pressure–lowering effects of fish oils.

Methods and Results—With a double-blind, placebo-controlled trial of parallel design, 59 overweight, mildly hyperlipidemic men were randomized to receive 4 g/d purified EPA, DHA, or olive oil (placebo) capsules while continuing their usual diets for 6 weeks. Forearm blood flow (FBF) was measured with venous occlusion, strain-gauge plethysmography during the sequential intra-arterial administration of acetylcholine (7.5, 15, and 30 μg/min), sodium nitroprusside (1.5, 3, and 10 μg/min), norepinephrine (10, 20, and 40 ng/min), a single-dose infusion of N\textsubscript{G}-monomethyl-L-arginine (L-NMMA) (1 mg/min), and coinfusion of acetylcholine (7.5, 15, and 30 μg/min) and L-NMMA. Forty of the 56 subjects who completed the study underwent FBF measurements. Plasma phospholipid EPA levels increased significantly (P<0.0001) after supplementation with EPA, and DHA composition increased with DHA supplementation (P<0.0001). Relative to placebo, DHA, but not EPA, supplementation significantly improved FBF in response to acetylcholine infusion (P<0.040) and coinfusion of acetylcholine with L-NMMA (P<0.040). Infusion of L-NMMA alone showed no group differences. DHA significantly enhanced dilatory responses to sodium nitroprusside (P<0.0001) and attenuated constrictor responses to norepinephrine (P=0.017).

Conclusions—Relative to placebo, DHA, but not EPA, enhances vasodilator mechanisms and attenuates constrictor responses in the forearm microcirculation. Improvements in endothelium-independent mechanisms appear to be predominant and may contribute to the selective blood pressure–lowering effect observed with DHA compared with EPA in humans. 

Key Words: fish oils • vasculature • blood pressure • nitric oxide • microcirculation

Experimental, clinical, and some epidemiological observations suggest that fish oils protect against cardiovascular disease.1 Mechanisms include improvements in vascular function secondary to the favorable effects of fish oils on blood pressure (BP),2,3 lipid4 and prostanoid1 metabolism, and thrombosis.5 Vascular function improves after ω3 fatty acid supplementation in experimental models of endothelial dysfunction,6–9 in normal healthy subjects,10–13 in hypercholesterolemic patients,14 and in type 2 diabetics.15

The principal ω3 fatty acids in fish oils are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Although studies in rats have demonstrated differential effects of EPA and DHA on vascular function,16,17 their effects on vascular and endothelial functions in humans have not been investigated. There is indirect evidence in humans, based on the urinary excretion of NO metabolites, that DHA may enhance endothelial function compared with EPA.18

We have reported that in overweight subjects with mild dyslipidemia, DHA significantly decreased arterial BP and heart rate compared with EPA19 and was accompanied by significant increases in LDL particle size and HDL2 cholesterol (HDL\textsubscript{2}-C). Hypertension, small LDL particle size, and low HDL\textsubscript{2}-C level are associated with endothelial dysfunction in humans.20 We proposed that relative to placebo, DHA would lead to greater improvements than EPA on forearm vasoactive responses in overweight subjects with dyslipid-
emia. Endothelium-dependent and -independent vascular function was studied with measurements of vasoreactivity to intra-arterial infusions of acetylcholine, releasing NO endogenously to produce vasodilation; to sodium nitroprusside, acting as a direct NO donor; and to norepinephrine, causing vasconstriction by activating α-adrenergic receptors on smooth muscle cells.21

Methods
Study Population
Subject characteristics have been described elsewhere.20 Briefly, mildly hyperlipidemic but otherwise healthy; nonsmoking men aged 20 to 65 years were recruited from the general community through media advertisements. Entry criteria included cholesterol level of ≥6 mmol/L or triglyceride level of ≥1.8 mmol/L (or both), body mass index (BMI) of 25 to 30 kg/m2, and no recent (within 3 months) symptomatic heart disease, diabetes mellitus, or liver or renal disease (plasma creatinine >130 μmol/L). Subjects were not on regular nonsteroidal anti-inflammatory drug therapy, antihypertensive drugs, lipid-lowering drugs, or other drugs that affect lipid metabolism. They had a usual weekly consumption of not more than 1 meal with fish and <210 mL of ethanol. Fifty-nine of 136 subjects who were screened satisfied the entry criteria. The study was approved by the Ethics Committee of the Royal Perth Hospital, and all subjects gave written consent.

Dietary Education and Intervention
Baseline measurements were collected for a 3-week period, during which subjects continued their usual diet and alcohol intake. They were matched for age and BMI and randomly assigned to 1 of 3 groups: EPA-ethyl ester (~96%), DHA-ethyl ester (~92%), or olive oil (~75% oleic acid ethyl ester) at 4 g/d for 6 weeks. Volunteers were asked to maintain their usual diets, alcohol intake, and physical activity and to not alter their lifestyle during the intervention. Subjects completed 3-day diet records at baseline and at the end of the intervention.19 Dietary and alcohol intake, physical activity, and use of medications were monitored every second week with the use of 7-day retrospective diaries.

Clinical Protocol for the Measurement of Forearm Vascular Reactivity
Studies were conducted in a vascular laboratory (ambient temperature 20° to 25°C), in the morning with subjects supine and having fasted for 12 hours. Subjects were studied twice: once before and once after the intervention. Resting BP was measured at baseline and at the end of the protocol with an automated recorder (Dinamap 845; Critikon). Forearm blood flow (FBF) was measured by venous occlusion plethysmography with mercury-in-Silastic strain gauges calibrated electronically (Hokanson EC 4 Plethysmograph; E.C. Hokanson, Inc.). During measurements, subjects had their left arm supported on the extensor aspect of the elbow joint on foam blocks in the same position on each occasion. The wrist cuff was inflated to 180 mm Hg for 1 minute to occlude blood flow to the hands. The upper arm cuff was inflated to 40 mm Hg to occlude venous return for 10 seconds and then deflated for 7 seconds for 4 cycles at a time, with FBF returning to baseline between cycles. Rapid cuff inflation was achieved with an air source coupled to 2 rapid cuff inflators (Hokanson E 20 Rapid Cuff Inflator; E.C. Hokanson, Inc.). Measurements were recorded on a Macintosh computer with the MacLab 3.3 program. Drugs or 0.9% saline was infused into the brachial artery of the left arm via a 20-gauge radial artery plastic cannula (Arrow) inserted under local anesthetic (2% procaine HCl).

Baseline measurements of FBF were recorded during a 15-minute infusion of 0.9% saline at 1 mL/min. This was followed by cumulative dosage infusions of acetylcholine (7.5, 15, and 30 μg/min), sodium nitroprusside (1.5, 3, and 10 μg/min), and norepinephrine (10, 20, and 40 ng/min). Drugs, diluted in 0.9% saline, were infused at 1 mL/min for 4 minutes with an infusion pump (Ivac 770 Syringe Pumps). FBF from each dose of infusion was measured during the fourth minute. Each drug infusion was interspersed with infusion of 0.9% saline at 1 mL/min for 15 minutes until blood flow returned to baseline. The specificity of the responses to NO was tested with a single dose of L-NMMA (1 mg/mL) infused at 1 mL/min for 8 minutes. This was followed by 4 minute co-infusions of L-NMMA and cumulative doses of acetylcholine (7.5,15 and 30 μg/min).

Calculations
Vascular responses were determined from the slope of each plethysmographic recording and expressed as mL blood flow · 100 mL−1 · min−1, where 100 mL−1 refers to forearm volume, as described by Whitney.21 The mean of the final 3 FBF measurements during the fourth minute of each drug infusion and the eighth minute of the L-NMMA infusion was then calculated. All traces were blindly analyzed by the same investigator.

Biochemical Analyses and Plasma Phospholipid Fatty Acids
Venous blood was collected with the subject in a semirecumbent position after a 12-hour fast: twice at baseline and twice at the end of the intervention. Serum for lipid, lipoprotein, and insulin levels was stored at −80°C and analyzed in a single assay to minimize interassay variation.22 Serum glucose level was measured with an automated immunoassay analyzer. Plasma phospholipid fatty acids were analyzed by gas liquid chromatography.22

Statistical Analysis
Diet records were analyzed with Diet/1 Version 4 (Xyris) based on the Australian Food Composition Database (NUTTAB 1995A).23 Responses to each drug were summarized with calculation of slopes of the regression lines that related dose and percentage response from baseline for each individual.24 Estimated slopes were used in subsequent analysis to examine the effect of treatment group on change in slope for each drug infusion before and after intervention. The study had a 70% power to detect a 0.30 mL · 100 mL−1 · min−1 difference in the slope, based on FBF responses to infusion of acetylcholine. Data were analyzed with SPSS (SPSS Inc) with general linear models (GLM) adjusted for baseline values. P<0.05

Baseline Characteristics of Subjects by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Olive Oil (n=14)</th>
<th>EPA (n=13)</th>
<th>DHA (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.8±2.0</td>
<td>49.1±2.5</td>
<td>50.6±1.4</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>86.7±2.3</td>
<td>89.1±2.1</td>
<td>92.2±3.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.9±0.5</td>
<td>29.2±0.7</td>
<td>29.2±0.7</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.93±0.01</td>
<td>0.95±0.01</td>
<td>0.94±0.01</td>
</tr>
<tr>
<td>24-h blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>121.5±3.5</td>
<td>124.2±3.2</td>
<td>122.5±3.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70.3±1.7</td>
<td>73.8±2.1</td>
<td>70.9±1.6</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.44±0.21</td>
<td>6.35±0.30</td>
<td>6.36±0.21</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.94±0.26</td>
<td>2.01±0.26</td>
<td>2.26±0.53</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>4.38±0.19</td>
<td>4.42±0.29</td>
<td>4.47±0.19</td>
</tr>
<tr>
<td>LDL particle size, nm</td>
<td>25.69±0.19</td>
<td>25.66±0.11</td>
<td>25.70±0.13</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.16±0.08</td>
<td>1.00±0.05</td>
<td>0.98±0.04</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>0.36±0.05</td>
<td>0.26±0.03</td>
<td>0.26±0.03</td>
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<tr>
<td>HDL-C, mmol/L</td>
<td>0.80±0.44</td>
<td>0.74±0.05</td>
<td>0.72±0.03</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.90±0.15</td>
<td>5.09±0.12</td>
<td>5.23±0.15</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>8.90±1.50</td>
<td>9.57±1.06</td>
<td>10.25±1.22</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Baseline measures did not differ significantly by ANOVA.
was considered significant with Bonferroni’s adjustment for multiple comparisons. Vasoconstrictor responses to norepinephrine were not normally distributed, and analysis was made with the Kruskal-Wallis test. Values are mean±SEM.

Results

Fifty-six of the 59 subjects who entered the study completed the 6-week intervention.19 Withdrawals were primarily due to inability to maintain the schedule of laboratory visits or to comply with the capsules. One subject withdrew due to gastrointestinal symptoms. Drug infusion studies were performed before and after intervention in 40 subjects who agreed to undertake the procedure. Baseline characteristics of the 3 groups are shown in the Table; there were no significant differences between the groups for any of the variables at baseline.

Weight did not change significantly during the intervention.19 Adherence to the diets was assessed with diet records, capsule counts, and changes in plasma phospholipid fatty acids.19 Total energy and major macronutrient intake were not significantly different between groups at baseline and did not change during the intervention.19

Forearm Vascular Reactivity

FBF in response to saline infusions before each of the cumulative dosage infusions of acetylcholine, sodium nitroprusside, norepinephrine, and L-NMMA at baseline and after the intervention was not significantly different between groups; there were no significant differences within each group between baseline and postintervention responses to the saline infusions.

During preintervention, FBF showed no significant differences between groups in the slopes of the lines in response to infusions of acetylcholine, sodium nitroprusside, norepinephrine, L-NMMA, or L-NMMA coinusions with acetylcholine, after adjustment for blood flow during the baseline saline infusion.

Acetylcholine and L-NMMA–Plus–Acetylcholine Infusions

The change in FBF in response to acetylcholine differed significantly between groups (P=0.047) (Figure 1). Relative to the olive oil group, DHA supplementation increased vasodilatory responses by 0.39 mL·100 mL⁻¹·µg⁻¹ (P=0.040), whereas EPA had no effect (P=0.244).

Before the intervention, the infusion of L-NMMA significantly reduced FBF relative to saline in the olive oil (−27%, P<0.0001), EPA (−23%, P<0.0001), and DHA (−24%, P=0.002) groups. After intervention, L-NMMA reduced FBF by 23% (P=0.008) in the olive oil group, 27% (P=0.002) in the EPA group, and 24% (P=0.003) in the DHA group. There were no significant differences in the response to L-NMMA between before and after interventions within treatment groups.

After intervention, the coinfusion of L-NMMA with acetylcholine attenuated FBF compared with the effects of acetylcholine alone (P=0.054), and the response differed significantly between groups (P=0.043) (Figure 2). Relative to olive oil, EPA supplementation had no significant effect (P=0.347), whereas DHA significantly enhanced dilatory responses by 0.29 mL·100 mL⁻¹·µg⁻¹ (P=0.040).

Sodium Nitroprusside Infusions

Forearm vasodilatory responses to sodium nitroprusside were significantly altered by the treatments (P=0.001) (Figure 3). DHA supplementation improved dilatory responses by 0.27 mL·100 mL⁻¹·µg⁻¹ (P<0.0001), but EPA did not change responses significantly (P=0.228), relative to the olive oil group.

Norepinephrine Infusions

There was significant attenuation (P=0.039) of the constrictor responses to DHA (0.28 mL·100 mL⁻¹·µg⁻¹, P=0.017), but not EPA (P=0.125), relative to the olive oil group (Figure 4).

Serum Lipids, LDL Particle Size, and Glucose and Insulin Levels

None of these variables changed significantly with olive oil supplementation. Neither EPA nor DHA supplementation affected serum total cholesterol. After adjustment for baseline values, fasting triglycerides fell by 18.4% with EPA (0.34±0.18 mmol/L, P=0.068) and by 20% with DHA (0.53±0.18 mmol/L, P=0.006), relative to the olive oil group. Serum LDL-C increased by 8% with DHA.
(0.26±0.10 mmol/L, P=0.013) but not with EPA. In the EPA group, a small decrease in HDL-C (0.06±0.03 mmol/L, P=0.064) resulted from a reduction in HDL 3-C (0.05±0.03 mmol/L, P=0.084). Although HDL-C was not significantly altered after DHA supplementation, HDL 2-C increased 29% (0.07±0.03 mmol/L, P=0.014). Relative to the olive oil group, DHA, but not EPA, increased LDL particle size (0.26±0.10 nm, P=0.013) after adjustment for baseline values.

There was no change in fasting glucose concentration with either EPA or DHA relative to the olive oil group, after adjustment for baseline values. Both EPA and DHA increased fasting insulin (1.70±0.94 pmol/L, P=0.078 [18%], and 2.53±0.93 pmol/L, P=0.010 [27%], respectively), relative to olive oil.

**Discussion**

The highly purified preparations used in the present study clearly distinguished between the effects of EPA and DHA, the 2 major ω3 fatty acids in fish and most fish oil preparations. The novel finding is that relative to placebo, DHA, but not EPA, improves vasodilator responses to endogenous and exogenous NO donors and attenuates vasoconstrictor response to norepinephrine in the forearm microcirculation of overweight subjects with hyperlipidemia. Mechanisms appear to be predominantly endothelium independent, based on enhanced vasodilatory responses after the coinfusion of acetylcholine with L-NMMA and the infusion of nitroprusside, both of which are endothelium independent. Our results, however, do not preclude some endothelial component in the dilatory responses associated with DHA. These findings may account for the lower BP observed after DHA supplementation.

The favorable effects seen with DHA were paralleled by changes in plasma lipid and lipoprotein levels. ω3 Fatty acids affect endothelial function, vascular reactivity, and BP. Fish oils have antihypertensive effects, which are possibly attributable to DHA and not EPA. These effects may be related to ω3 fatty acid–induced changes in vasoreactivity, which is consistent with our findings that fish oils fed to hypertensive rats increased endothelial relaxation in response to acetylcholine in aortic rings and decreased pressor reactivity of perfused mesenteric resistance vessels. Increased endothelial relaxation related at least in part to suppression of thromboxane A2 or cyclic endoperoxides, as well as enhanced endothelial NO synthesis. In humans, fish oils reduced forearm vascular reactivity to angiotensin II and norepinephrine, effects that were antagonized by the oral administration of indomethacin, suggesting the involvement of cyclooxygenase-derived prostanooids. Indomethacin alone did not affect responses. Fish oils have little effect on the vasodilation induced by acetylcholine or reactive hyperemia in forearm resistance arteries of healthy subjects. However, ω3 fatty acids restore impaired responses to endothelium-dependent vasodilators in patients with coronary artery disease, as well as in animal models characterized by endothelial damage. Chin and Dart demonstrated that dietary fish oils enhanced vasodilatory responses to acetylcholine in hypercholesterolemic subjects without affecting total cholesterol.
Fish oils improved forearm vasodilator responses to acetylcholine, but not to glyceryltrinitrate, in type 2 diabetics, suggesting that ω3 fatty acids may protect against vasoconstriction and thrombosis by enhancing NO release and suppressing thromboxane formation. Further evidence that fish oils may affect the production or release of NO comes from studies that showed enhanced responses to endothelium-dependent vasodilators such as Bradykinin, serotonin, ADP, and thrombin in rings of coronary arteries taken from pigs fed cod liver oil. Responses were unaltered by indomethacin or nitroprusside, confirming that the augmentation was independent of vasodilator prostaglandins and changes in smooth muscle cells.

Despite the plethora of studies concerning ω3 fatty acids, to date there is no information on the relative effects of pure EPA or DHA on endothelial or vascular smooth muscle function in humans. Engler et al reported that in aortic rings from spontaneously hypertensive rats and Wistar-Kyoto rats, EPA and DHA induced endothelium-dependent and -independent vasodilation, respectively. McLennan et al demonstrated that DHA was also more effective than EPA at inhibition of thromboxane-like vasoconstrictor responses in the aortas from spontaneously hypertensive rats. The authors postulated that DHA may prevent thromboxane-induced contraction and perhaps restore the vasoconstrictor/vasodilator balance after impairment of the normal NO-related processes. Whether DHA inhibits thromboxane synthetase or thromboxane A2/prostaglandin H2 receptor function remains unresolved. Hashimoto et al have shown that rats fed DHA intragastrically had reduced plasma norepinephrine levels. Increased adenylyl purines such as ATP, released both spontaneously and in response to norepinephrine from segments of caudal artery, were significantly inversely associated with BP. ATP causes vasodilation by stimulating the release of NO from endothelial cells, via a direct action on vascular smooth muscle cells, and by hyperpolarizing smooth muscle cells. DHA was postulated to alter membrane fatty acid composition and accelerate ATP release from vascular endothelial cells, which, in conjunction with reduced plasma norepinephrine, may be responsible for the fall in BP.

The favorable effects seen on vasoreactivity with DHA are likely to be mediated by multiple mechanisms, predominantly endothelial-independent mechanisms. These may be attributable to direct and indirect effects of DHA on the arterial wall. The selective incorporation of DHA into endothelial membranes could increase membrane fluidity, calcium influx, and endogenous synthesis and NO release. However, the lack of a significant difference in the basal blood flow response to L-NMMA argues against a specific effect of DHA on basal synthesis and NO release. A direct effect on receptor-stimulated NO release may account for the improved response to acetylcholine. However, the results of the coinfusion of acetylcholine plus L-NMMA indicate that DHA may enhance the release of vasodilator prostanooids or endothelium-derived hyperpolarizing factor, consistent with experimental evidence. The enhanced vasodilator response to sodium nitroprusside may be due to increased biotransformation to NO or increased reactivity of smooth muscle cells to vasorelaxation consequent to decreased calcium influx, as reported elsewhere with fish oils. These mechanisms, as well as the increased release of a vasodilator cyclooxygenase metabolite, may also account for the decreased vasoconstriction to norepinephrine.

The reduction in VLDL seen with fish oils may mediate improvement in endothelial function, but because plasma triglyceride changes were similar in EPA- and DHA-treated patients, VLDL changes cannot account for the effects of DHA. Small, dense LDL is more susceptible to oxidative modification than large LDL, and in modified form, it impairs the function of NO synthase and converts NO to peroxynitrite. Increased LDL size in patients who take DHA could explain the improved vasoreactivity. Because HDL has antioxidant properties and may directly improve endothelial function, the increase in HDL-C may also have contributed to favorable effects with DHA. Insulin releases NO from endothelial cells and attenuates vasoconstriction due to adrenergic stimuli, but changes in insulin sensitivity are an unlikely explanation, because the plasma insulin-to-glucose ratio did not differ significantly between EPA and DHA.

The induction of NO synthase in vascular smooth muscle cells is inhibited by mitogens such as platelet-derived growth factor. DHA may increase basal production of NO in smooth muscle cells as a consequence of decreased release of PDGF from platelets. Regardless of the mechanisms responsible for the vascular benefits seen with DHA in the present study, it remains to be established why these do not operate with the administration of EPA. A more selective appraisal of the mechanisms of the effect of DHA could be achieved with α1-adrenergic receptor and angiotensin II receptor antagonists or prostaglandin synthesis inhibitors.

We saw no significant correlations between FBF and serum lipid, glucose, and insulin levels or BP in within-group
analyses. The lack of correlation between vasodilator and vasoconstrictor responses and BP changes with DHA suggests independent mechanisms. However, vascular responses could be secondary to improvements in BP with DHA, involving an undefined mechanism. DHA, but not EPA, reduced heart rate,\(^9\) raising the possibility of a significant cardiac contribution to the fall in BP. The effects of fish oils in increasing aortic compliance and leading to BP reduction might also be expected in animal studies.\(^8\)

The present study has demonstrated that in overweight, mildly hyperlipidemic men, DHA, but not EPA, enhances vasodilator responses relative to olive oil in the microcirculation of the forearm to both endogenous and exogenous NO donors via predominantly endothelial-independent mechanisms and attenuates constrictor responses to norepinephrine. These vasoactive effects may in part contribute to the BP-lowering actions of DHA. These observations are relevant to the food industry with respect to the incorporation of \(\alpha\) fatty acids into foodstuffs and animal feeds and, hence, the human food chain.

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References
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