Marine Oils Dose-Dependently Inhibit Vasoconstriction of Forearm Resistance Vessels in Humans

Jaye P.F. Chin, Anthony P. Gust, Paul J. Nestel, and Anthony M. Dart

The effects of dietary supplementation with marine oils on vascular reactivity in human forearm resistance arteries were studied. Healthy male adults (six to nine subjects per group) were given either maxEPA capsules (content: eicosapentaenoic acid, 0.178 g/g; docosahexaenoic acid, 0.116 g/g) at doses of 20, 10, or 5 g/day or placebo capsules at 20 g/day for 28 days. Capsule compliance was confirmed by measurement of platelet membrane incorporation of n-3 fatty acids. Blood pressure was not affected by either maxEPA or placebo. The influence of treatment interventions on forearm vasoconstrictive responses to local infusions of angiotensin II and norepinephrine was examined using venous occlusion plethysmography before and after treatment. Responses to both agonists were significantly suppressed by 20 g/day maxEPA (slopes before and after maxEPA, respectively: angiotensin II, 3.34 and 0.89; norepinephrine, 0.91 and 0.41). When analyzed as difference in area under the dose–response curves, the suppressive effects of maxEPA were clearly dose dependent (angiotensin II: 20 g area reduced by 72%, 10 g by 67%, 5 g by 33%). Similarly, responses to norepinephrine were dose-dependently suppressed by maxEPA (20 g area reduced by 61%, 10 g by 63%, and 5 g by 33%). Placebo had no effect on the responses to either constrictor. The responses to both agonists returned to preoil levels after 2 months’ discontinuation of 20 g/day maxEPA. We conclude that the suppressive effects of marine oils on vascular reactivity may, in part, contribute to their cardioprotective influence in humans. (Hypertension 1993;21:22-28)

KEY WORDS • n-3 polyunsaturated fatty acids • forearm resistance arteries • blood pressure • human studies

Dietary supplementation with n-3 polyunsaturated fatty acids of marine origin is widely reported to exert a range of biological effects of relevance to cardiovascular disease. Their protective effects include the ability to lower plasma lipids, in particular triglycerides and very low density lipoproteins1,2; to decrease production of the platelet aggregating factor thromboxane A23 and its product β-thromboglobulin4; and to lower blood pressure in subjects with hypercholesterolemia5,6 and in patients with essential hypertension6,7.

In the present study, we investigated whether dietary supplementation with marine oils induces changes in vascular reactivity that may contribute to their cardioprotective effect. This hypothesis follows reports of attenuated constrictor responses to norepinephrine in vessels isolated from spontaneously hypertensive rats fed marine oils8 as well as reduced constrictor responses to norepinephrine and angiotensin II in isolated perfused rabbit ear artery preparations in the presence of eicosapentaenoic acid, a major constituent of marine oils.9 Similar findings have also been reported in humans, in which a reduction in whole-body pressor responses to angiotensin II was observed after treatment with marine oils.4 In this study, a direct assessment of the influence of marine oils on vascular reactivity in humans is made using forearm venous occlusion plethysmography.

Methods

Subjects

Twenty-nine healthy adult males (18–32 years old) were recruited to participate in the study. Criteria for inclusion in the study included nonsmoking status, absence of alcohol abuse (less than two standard alcohol drinks per day), systolic blood pressure <140 and diastolic blood pressure <90 mm Hg, total serum cholesterol <5.5 mmol/l, and total triglyceride <2.0 mmol/l. In addition, all volunteers had normal findings on physical examination as well as routine hematology and biochemical blood analyses.

The protocol used was approved by the Alfred Group of Hospitals Ethics Committee, and written informed consent was obtained from all subjects.

Marine Oil Supplementation

A single-blind, placebo-controlled study design was used. All subjects were instructed to maintain, during oil supplementation, their preoil supplementation lifestyles. A parallel rather than crossover protocol was used because of our previous demonstration that a long

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washout period was required (>20 weeks) after discontinuation of maxEPA for platelet membrane incorporation of n-3 fatty acids to return to baseline values.2

Subjects were randomly allocated to one of four different groups. Each subject was treated for 28 days with either 1) 20 g/day maxEPA capsules (eicosapentaenoic acid [EPA], 0.178 g/g; docosahexaenoic acid, 0.116 g/g; see Table 1; n=6), 2) 10 g/day maxEPA capsules (n=6), 3) 5 g/day maxEPA capsules (n=8), or 4) 20 g/day mixed oil placebo (MOP) capsules (see Table 1; n=9).

The MOP capsules were carefully formulated to contain approximately equivalent concentrations of saturated fatty acids and monoenes to the maxEPA capsules. The polyunsaturated/saturated ratio was similar for both capsules, as was the caloric load. Antioxidants were present in both MOP and maxEPA capsules (a-tocopherol in maxEPA and tert-butylhydroquinone in the MOP capsules, as this was inherent in the celestial oil compound).

**Experimental Protocol**

Subjects rested supine throughout the course of the experiment in a comfortable, relaxing environment maintained at a constant temperature of 22°C. Measurements of forearm vessel constriction were made both before (day 1) and after (day 29) each treatment intervention. Four subjects on the 20 g/day maxEPA regimen returned experiment in a comfortable, relaxing environment maintained at a constant temperature of 22°C. Measurements of forearm vessel constriction were made both before (day 1) and after (day 29) each treatment intervention.

Forearm blood flow was measured by venous occlusion plethysmography with a sealed, alloy-filled (gallium indium), double-strand strain gauge (Medasonic, Mountain View, Calif.). Venous occlusion pressure was 40–50 mm Hg at the proximal (elbow) end, and cuff occlusion pressure at the distal (wrist) end approximated 200 mm Hg. Forearm blood flow was recorded for 10 out of every 20 seconds. The mean flow values of three to five measurements before and after drug infusion were used for analyses.

The brachial artery was cannulated (3.0F, 5-cm catheter; Cook, Australia) for intra-arterial pressure recording as well as for local, sequential infusions of norepinephrine (25, 50, and 100 ng/min) and angiotensin II (8, 16, and 32 ng/min). Each concentration was infused at 4 ml/min over 2 minutes. Rest periods of 5 minutes between concentrations and 15 minutes between drugs were observed. Physiological saline (0.9%) was infused when baseline measurements were made. The lack of systemic vasoconstrictor effect was confirmed by constant central hemodynamic monitoring (heart rate via electrocardiographic lead II and blood pressure; Spacelabs Inc., Wash.). Arterial blood pressure was recorded with an AE 840 physiological pressure transducer throughout the course of each experiment. Resting blood pressure was recorded 30 minutes after the cannulation procedure, before the start of flow measurements.

Forearm vascular resistance (FVR) was calculated from the equation

\[
\text{FVR (R units)} = \frac{\text{mean arterial pressure (mm Hg)}}{\text{forearm blood flow (ml/100 ml/min)}}
\]

Because a high within-subject coefficient of variation (range, 0.02–0.47; mean, 0.19±0.02; see Table 3) was observed on basal forearm vascular resistance, the response to each concentration of the agonists used was compared with the basal forearm vascular resistance obtained immediately before the administration of each dose.

Similarly, because a high between-subject (pretreatment) variation of basal forearm vascular resistance values (range, 26.9–79.1 FVR units) was observed, responses were analyzed as a percent of basal responses.

**Platelet Membrane Fatty Acids**

The incorporation of n-3 fatty acids into platelet membranes was analyzed both to monitor volunteer compliance in capsule consumption and to assess the effects of the varying maxEPA doses in changing membrane fatty acid composition. Forty milliliters of blood was taken from each subject after each treatment intervention and was placed into Tris-buffered tubes before separation of platelets by centrifugation. Platelet pellets thus obtained were stored in aqueous form (in 1 ml saline) at −70°C until batched and transported on dry ice to the CSIRO Division of Human Nutrition, Adelaide. Platelet fatty acids were subsequently transesterified and methylated, and the methyl esters were analyzed by gas chromatography with a capillary column.10 Results are given as percent of total platelet membrane fatty acid pool for eicosapentaenoic acid, docosahexaenoic acid, and arachidonic acid.

**Statistical Analysis**

Results are expressed as mean±SEM or standard error of the difference (SED) when appropriate. Statistical analysis was by Student’s t test (paired when required). A value of p<0.05 was used as the criterion for statistical significance.

Lines of best fit were calculated for each group of agonist dose–response curves both before and after each treatment intervention. Comparisons of appropriate regression lines were then made using an analysis of covariance for comparisons of slopes and elevations.11 A recommended method of analysis, the method of summary measures,12 was also undertaken for further analysis of dose–response curves, because there was a strong dependency between measurements within the same patient. A summary measure was obtained by calculation of the area under each individual dose–response (%FVR) curve12 obtained before and after each treatment intervention. Analysis performed by area under the curve gave the added advantage of a
Drugs Used
MOP and maxEPA capsules were from RP Scherer, Australia. Norepinephrine acid tartrate (Levophed; Winthrop, Australia) and angiotensin II (Hypertensina Australia. Norepinephrine acid tartrate (Levophed; Winthrop, Australia) and angiotensin II (Hypertensina CIBA; CIBA-GEIGY, Switzerland) were diluted to the treatments used.

Comparison of the dose-dependent effects of the direct comparison of the dose-dependent effects of the treatments used.

Results

Platelet Membrane Fatty Acids
Platelet membrane incorporation of the n-3 polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid dose-dependently increased with maxEPA supplementation (Table 2). Compared with levels obtained from subjects on the placebo supplementation, combined eicosapentaenoic acid and docosahexaenoic acid levels increased by approximately 103% in subjects on the 5 g/day maxEPA regimen, by 230% in those on the 10 g/day maxEPA regimen, and by 246% in those on the 20 g/day regimen. Incorporation of arachidonic acid was not affected by treatment.

Blood Pressure
Table 2 summarizes resting blood pressure results. Dietary supplementation with maxEPA, irrespective of treatment regimen used, had no effect on either systolic or diastolic blood pressure. MOP similarly had no effect on blood pressure.

Mean arterial pressure and heart rate monitored during the course of each experiment confirmed that, at the concentrations used, neither norepinephrine (mean arterial pressure: before norepinephrine versus 100 ng/min norepinephrine, 85.7±1.23 versus 86.7±1.58 mg; n=29 subjects, p>0.05) nor angiotensin II had any systemic vasoconstrictor or reflex action.

Basal Forearm Blood Flow
With the exception of maxEPA at 10 g/day, basal forearm blood flow measurements were not altered after oil supplementation. MaxEPA at 10 g/day for 28 days significantly decreased basal forearm blood flow levels from 3.61±0.45 to 1.54±0.25 ml/100 ml/min (paired Student’s t test, p<0.05). Correspondingly, forearm vascular resistance values increased significantly after 10 g/day maxEPA (before versus after oil: 30.12 versus 68.89, SED=11.83).

Forearm Vascular Reactivity
Table 3 shows the effects of the treatments used on forearm vascular resistance measurements obtained immediately before and during each infusion of norepinephrine. Treatment with 20 g/day maxEPA significantly attenuated the responses to norepinephrine when expressed as percent difference in forearm vascular resistance (Figure 1A). The area under the dose-response curve (AUC) obtained to norepinephrine decreased by 60.6±3.4% (Figure 2A; AUC before versus after maxEPA, 4,159.9±620.8 versus 1,576.1±116.6 units, p<0.05) after supplementation with maxEPA. Analysis of the slopes of dose–response curves demonstrated a similar attenuated response to norepinephrine after 20 g/day maxEPA treatment (before versus after maxEPA, 0.91 versus 0.41, p<0.05). These responses returned to preoil levels after 2 months’ discontinuation of 20 g/day maxEPA (Figure 1A) and were unaltered by MOP (Figure 1B).

As previously mentioned, basal forearm blood flow decreased after 10 g/day maxEPA. This corresponded to an increase in basal forearm vascular resistance (see Table 3) and complicated interpretation of the results obtained to the vasoconstrictor norepinephrine. Responses to this agonist were attenuated when expressed as percent difference in forearm vascular resistance. However, a potentiating effect of 10 g/day maxEPA was observed at 100 ng/min norepinephrine when results were expressed as absolute difference in forearm vascular resistance. Analysis by the method of summary measures demonstrated a decrease of 63.4±9.4% in area under the dose–response curve to norepinephrine after 10 g/day maxEPA (Figure 2A). Analysis of slopes of the dose–response curve to norepinephrine demonstrated a similar attenuation in response after 10 g/day maxEPA (before versus after maxEPA, 0.72 versus 0.38).

Responses to norepinephrine were also attenuated after the 5 g/day maxEPA regimen. This attenuation can be summarized as a 33.4±20.3% decrease when expressed as area under the dose–response curve to norepinephrine (Figure 2A).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (20 g/day) (n=9)</th>
<th>5 g/day (n=8)</th>
<th>10 g/day (n=6)</th>
<th>20 g/day (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPA (% total)</td>
<td>0.78±0.29</td>
<td>2.31±0.17*</td>
<td>4.46±0.18*</td>
<td>6.95±0.64*</td>
</tr>
<tr>
<td>DHA (% total)</td>
<td>1.48±0.07</td>
<td>2.5±0.14*</td>
<td>3.36±0.12*</td>
<td>4.23±0.31*</td>
</tr>
<tr>
<td>AA (% total)</td>
<td>12.6±1.18</td>
<td>11.18±1.09</td>
<td>11.97±0.56</td>
<td>13.77±2.19</td>
</tr>
</tbody>
</table>

Systolic blood pressure

| Before treatment (mm Hg) | 124.0±4.03               | 122.8±4.42    | 125.8±2.57     | 131.0±8.07     |
| After treatment (mm Hg)  | 126.5±2.78               | 125.6±6.01    | 125.0±2.67     | 130.0±6.27     |

Diastolic blood pressure

| Before treatment (mm Hg) | 65.2±1.31                | 65.3±2.17     | 67.0±1.21      | 68.8±2.84      |
| After treatment (mm Hg)  | 64.5±2.99                | 66.0±2.16     | 66.5±2.13      | 69.2±1.88      |

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid. Values are mean±SEM. *p<0.05, compared with placebo levels, Student’s t test.
Table 3. Effects of Treatment Regimens on Responses of Forearm Vascular Resistance to Norepinephrine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Norepinephrine (25 ng/min)</th>
<th>Norepinephrine (50 ng/min)</th>
<th>Norepinephrine (100 ng/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FVR&lt;sub&gt;b&lt;/sub&gt;</td>
<td>FVR&lt;sub&gt;oc&lt;/sub&gt;</td>
<td>a. diff</td>
</tr>
<tr>
<td>Placebo Before</td>
<td>47.8</td>
<td>54.7</td>
<td>6.9</td>
</tr>
<tr>
<td>After</td>
<td>46.9</td>
<td>50.9</td>
<td>4.0</td>
</tr>
<tr>
<td>SED</td>
<td>10.6</td>
<td>11.0</td>
<td>2.7</td>
</tr>
<tr>
<td>5 g/day maxEPA</td>
<td>Before</td>
<td>79.1</td>
<td>86.4</td>
</tr>
<tr>
<td>After</td>
<td>79.2</td>
<td>71.7</td>
<td>-7.5</td>
</tr>
<tr>
<td>SED</td>
<td>19.6</td>
<td>15.2</td>
<td>7.1</td>
</tr>
<tr>
<td>10 g/day maxEPA</td>
<td>Before</td>
<td>43.6</td>
<td>51.1</td>
</tr>
<tr>
<td>After</td>
<td>73.9</td>
<td>74.2</td>
<td>0.3</td>
</tr>
<tr>
<td>SED</td>
<td>14.1</td>
<td>14.6</td>
<td>3.8</td>
</tr>
<tr>
<td>20 g/day maxEPA</td>
<td>Before</td>
<td>26.9</td>
<td>36.2</td>
</tr>
<tr>
<td>After</td>
<td>40.1</td>
<td>50.5</td>
<td>6.2</td>
</tr>
<tr>
<td>SED</td>
<td>13.9</td>
<td>18.0</td>
<td>5.1</td>
</tr>
</tbody>
</table>

FVR<sub>b</sub>, mean basal forearm vascular resistance; FVR<sub>oc</sub>, mean FVR during norepinephrine infusion; a. diff, mean absolute difference between FVR during norepinephrine and at rest; % diff, mean percent difference between FVR during norepinephrine and at rest; SED, standard error of difference. maxEPA treatment at 5, 10, and 20 g/day was for 28 days.

Table 4 shows forearm vascular resistance measurements obtained immediately before and during each infusion of angiotensin II for each treatment regimen. Dietary supplementation with 20 g/day maxEPA for 28 days significantly suppressed the three-point dose-response curve to angiotensin II (Figure 3A; slope before versus after maxEPA, 3.2 versus 0.9, p<0.05). When analyzed as area under the dose-response curves, dietary supplementation with 20 g/day maxEPA suppressed the response to angiotensin II by 71.8±9.0% (Figure 2B; AUC before versus after maxEPA, 1,971.4±253.9 versus 607.2±200.1 units, p<0.05). In the four subjects who returned after a 2-month washout period, responses to angiotensin II returned to preoil levels (Figure 3A). Responses to angiotensin II were also significantly suppressed by maxEPA at the lower doses of 10 g/day (by 67.1±4.0% when analyzed as AUC, p<0.05, Figure 2B) and 5 g/day (by 33.5±17.5%, p<0.05, Figure 2B). MOP supplementation (20 g/day for 28 days, Figure 3B) had no effect on responses to angiotensin II.

Discussion

In the present study, forearm vasoconstrictor responses to the sympathetic nervous system neurotransmitter norepinephrine and the renin-angiotensin system effector angiotensin II were markedly attenuated after dietary supplementation with marine oils. One strength of the study lies in the null effect seen after placebo supplementation, which confirms that the decreased responses to both agonists seen with marine oils were not a result of habituation of the study protocol, changed caloric intake, or differences in polyunsaturated/saturated ratio. The findings are further substantiated by the return to normal (before maxEPA) responses seen with both constrictors after the 2-month washout period. Although the placebo capsules were...
the observation that marine oils lower the peak pressures induced by the endogenous stressors angiotensin II² and norepinephrine, thus protecting against cardiovascular dysfunction related to high levels of these agonists. The modification by marine oils in responses to the effectors of the sympathetic nervous system and the renin-angiotensin system, both of which have been reported to contribute to the development of hypertension, may also, in part, underlie epidemiological reports of lower incidences of hypertension in populations with high fish consumption.¹⁷

The blood pressure-lowering effect of marine oils, previously reported in several other papers, was not observed in the present study. A closer examination of the literature, however, reveals that a hypotensive effect of marine oils appears to be present only in subjects with high blood pressure, or hypercholesterolemia, and not in healthy, normocholesterolemic, normotensive subjects or subjects with controlled (treated) hypertension. It has previously been suggested that the blood pressure response to marine oils is dependent on the initial blood pressure of the patient, and it is likely that any changes induced by marine oils on the blood pressure of normotensive subjects is too small to demonstrate significance, particularly in a parallel study design. That the blood pressure-lowering effect of marine oils has also been demonstrated, to date, only in normotensive subjects with hyperlipidemia suggests the interesting possibility that this effect is dependent on changes in circulating lipoproteins. The lack of effect of marine oils on blood pressure in the present study was not due to differences in dosage as compared with previous studies. Reported doses effective in lowering blood pressure in hypertensive and hypercholesterolemic patients vary, ranging from approximately 3.0 to 15 g of n-3 polyunsaturated fatty acids per day. In our study, the maximum dose of 20 g/day maxEPA (equivalent to n-3 polyunsaturated levels of 5.88 g/day) was

### TABLE 4. Effects of Treatment Regimens on Responses of Forearm Vascular Resistance to Angiotensin II

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Angiotensin II (8 ng/min)</th>
<th>Angiotensin II (16 ng/min)</th>
<th>Angiotensin II (32 ng/min)</th>
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<tr>
<td></td>
<td>FVR, FVR&lt;sub&gt;hit&lt;/sub&gt;</td>
<td>a. diff</td>
<td>% diff</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>52.9</td>
<td>66.9</td>
<td>11.4</td>
</tr>
<tr>
<td>After</td>
<td>45.7</td>
<td>51.6</td>
<td>6.8</td>
</tr>
<tr>
<td>SED</td>
<td>12.3</td>
<td>15.2</td>
<td>4.4</td>
</tr>
<tr>
<td>5 g/day maxEPA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>59.7</td>
<td>67.5</td>
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<tr>
<td>After</td>
<td>48.3</td>
<td>51.9</td>
<td>3.6</td>
</tr>
<tr>
<td>SED</td>
<td>6.3</td>
<td>8.1</td>
<td>15.5</td>
</tr>
<tr>
<td>10 g/day maxEPA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>26.0</td>
<td>37.1</td>
<td>11.1</td>
</tr>
<tr>
<td>After</td>
<td>53.0</td>
<td>61.1</td>
<td>8.1</td>
</tr>
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<td>SED</td>
<td>8.6</td>
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</tr>
<tr>
<td>20 g/day maxEPA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>36.6</td>
<td>48.0</td>
<td>11.4</td>
</tr>
<tr>
<td>After</td>
<td>46.9</td>
<td>56.9</td>
<td>10.0</td>
</tr>
<tr>
<td>SED</td>
<td>21.9</td>
<td>28.7</td>
<td>9.6</td>
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</table>

FVR<sub>r</sub>, mean basal forearm vascular resistance (FVR) obtained just before angiotensin II infusion; FVR<sub>hit</sub>, mean FVR during angiotensin II infusion; a. diff, mean absolute difference between FVR during angiotensin II and at rest; % diff, mean percent difference between FVR during angiotensin II and at rest; SED, standard error of difference. maxEPA treatment 5, 10, and 20 g/day was for 28 days.
ineffective in reducing blood pressure in normotensive subjects. Because blood pressure was unaltered in these subjects, we suggest that the changes observed with marine oils, seen only on drug-induced vasoconstriction, is consistent with a more efficacious effect of maxEPA on amplified vasoconstrictor responses seen in individuals with high blood pressure. This may underlie the more potent effect of maxEPA as a hypotensive agent in hypertensive patients compared with normotensive subjects.

The finding that 10 g/day maxEPA decreased forearm basal blood flow was unexpected and suggests that at this concentration marine oils may be exerting a chronic vasoconstrictor effect as evidenced by the increase obtained in basal forearm vascular resistance. The change in basal forearm resistance values induced by 10 g/day maxEPA rendered interpretation of the responses obtained to the vasoconstrictors used difficult; however, when results were expressed as a percentage of the basal responses obtained, 10 g/day maxEPA was observed to decrease the slope and area of the concentration–response curves obtained to both these agonists. At this concentration, therefore, vascular reactivity to both norepinephrine and angiotensin II is suppressed, although a potentiation to basal vascular resistance results was obtained. Because alteration of prostaglan-

din metabolism has no effect on forearm blood flow and because this effect was not seen with the other treatment doses used, it is difficult to resolve this concentration-dependent effect with current knowledge. It is noteworthy that a corresponding change in blood pressure was not seen in these subjects.

In the present study, the suppressive effect of marine oils on vasoconstriction induced by either norepinephrine or angiotensin II was demonstrated to be dose dependent. Because blood pressure was not affected at any of the treatment doses administered, we postulate that changes in vascular reactivity are primary and not secondary to any effects of blood pressure changes induced by marine oils. The dose-dependent suppressive effect of marine oils on vasoconstriction induced by these agonists may be responsible for the dose-dependent blood pressure–lowering effect of marine oils seen in patients with essential hypertension.

The mode by which marine oils exert their vasoconstrictor blunting effect was not studied in the current protocol. Changes in blood viscosity were not assessed but seem unlikely to have played a significant role in view of the lack of effect of the higher dose of maxEPA to influence resting blood flow. Because the responses to both norepinephrine acting on α-adrenergic receptors and angiotensin II acting on angiotensin II receptors were equally suppressed, we surmise that the effect is not receptor specific. Experiments performed in various animal models have suggested that this effect may instead be endothelium dependent or dependent on changes in the prostanoidal profile. It is also conceivable that, because platelet membrane composition was shown to alter with treatment, similar changes at the smooth muscle membrane level may affect receptor signaling at the second messenger level. Another possible mechanism for the changes in vascular reactivity observed may be as a result of changes in lipid profiles after marine oil supplementation, as was recently demonstrated in hypercholesterolemic patients. Future experiments must include a study of these possible mechanisms.

In summary, we have shown that marine oils dose-dependently suppress vasoconstrictive responses to norepinephrine and angiotensin II in human forearm resistance arteries and that these effects are reversible after a 2-month washout period. We suggest that this suppressive effect of marine oils on vascular reactivity may, in part, contribute to their cardioprotective influence in humans. The finding that maxEPA at 10 g/day decreased basal forearm blood flow was unexpected and is worthy of further examination.

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