Effects on Blood Pressure of \(\omega3\) Fats in Subjects at Increased Risk of Cardiovascular Disease

Robert Vandongen†, Trevor A. Mori, Valerie Burke, Lawrence J. Beilin, Jenny Morris, Jackie Ritchie

This study was conducted to compare the effects of \(\omega3\) fatty acids, taken as fish or fish-oil supplements in the setting of a high- or low-fat dietary background, on blood pressure and heart rate in men with moderate cardiovascular risks. One hundred twenty men were randomly allocated to five high-fat (40% of daily energy) and two low-fat (30% of energy) groups to undertake a 12-week dietary intervention period involving fish, fish oil, or a combination of these. Sodium intake was restricted to less than 90 mmol/d. The five high-fat groups were assigned to take either 6 or 12 fish-oil capsules daily, fish or a combination of fish oil and fish, or placebo capsules. The two low-fat groups took either fish or placebo capsules. Fish meals were devised to provide 1.3 g of eicosapentaenoic acid daily, equivalent to that contained in 6 fish-oil capsules. Subjects were instructed to eat a selection of fish that provided an average of 3.65 g/d (range, 3.2 to 4.1 g/d) of total \(\omega3\) fatty acids. Subjects were seen at regular intervals during the baseline and dietary intervention periods for measurement of weight, blood pressure, heart rate, dietary compliance, urine electrolyte excretion, platelet phospholipid fatty acids, blood glucose, and insulin concentration. There was a greater fall in both systolic and diastolic blood pressures in subjects allocated fish or fish oil, particularly in the low-fat groups, compared with control subjects. However, there was no significant group effect. For all groups combined, there were highly significant relations, independent of changes in weight and urinary sodium and potassium excretions, between the fall in blood pressure and the increase in \(\omega3\) and decrease in \(\omega6\) fatty acids in platelet phospholipids. The fall in heart rate observed in the fish and fish-oil-supplemented groups was significantly related to the changes in platelet \(\omega3\) and \(\omega6\) fatty acids. It is proposed that, in addition to previously reported alterations in platelet eicosanoid production, similar changes in fatty acid composition at the vascular and myocardial cellular levels result in the cardiovascular responses observed. (Hypertension. 1993;22:371-379.)

**KEY WORDS** • fatty acids, \(\omega3\) • blood pressure • platelets

There is growing evidence for potential benefits of dietary \(\omega3\) fatty acids of marine origin in terms of protection against coronary artery disease. These benefits are probably mediated at least in part by effects on platelet function and lipoprotein metabolism.\(^1\) The effects of \(\omega3\) fatty acids on blood pressure (BP) are less clear. Although some studies have clearly shown significant BP-lowering effects of fish-oil supplements, including the large Tromso study in untreated hypertensive subjects,\(^2\) an equally large North American study failed to demonstrate any such effect.\(^3\) Possible reasons for these discrepancies are differences in the background diets of the populations. For example, in the Tromso study, subgroup analysis showed a BP fall with fish oils only in those subjects eating less than three fish meals a week. Other explanations may be the higher baseline BP in the Tromso population and the larger doses of \(\omega3\) fats given to them.\(^2\) In addition to the fact that changes in BP after \(\omega3\) fatty acids are easier to detect in subjects with elevated BP, there is increasing evidence to suggest that these fatty acids may lower BP only in hypertensive subjects.\(^4\) Dietary sodium is another possible determinant of the response to fish oils, with animal data suggesting that in the presence of a high-sodium intake, fish-oil supplementation may even lead to BP elevation rather than reduction,\(^5\) whereas sodium restriction appears to amplify the BP reduction seen with fish oils in older subjects.\(^6\)

The present study was carried out to help determine optimal dietary regimens for minimizing cardiovascular risk with respect to BP, blood lipids, platelet function, and blood coagulation factors in otherwise healthy subjects whose BP levels and blood lipids exposed them to increased risk of cardiovascular disease. This report deals with the changes in BP and heart rate (HR) after dietary supplementation with \(\omega3\) fatty acids. It was specifically designed to ascertain if the effects on BP and HR were dependent on the form of \(\omega3\) fats, ie, as fish or fish oil, and on the presence of a low or high saturated fat diet.

**Methods**

**Recruitment and Dietary Education**

Men aged 30 to 60 years were recruited from the general community by media advertising. The aim was
to select subjects having a body mass index, BP, and serum cholesterol levels toward the higher end of the "normal" range. Respondents were invited to attend the Research Clinic on 3 separate days for screening measurements to determine suitability according to the following entry criteria: body mass index less than 33 kg/m², systolic BP 130 to 159 mm Hg, diastolic BP 80 to 99 mm Hg, serum cholesterol 5.2 to 6.9 mmol/L, non-smoking, not taking any medication, and having no significant illness or allergic disorder. Entry was also restricted to subjects eating one or less than one fish meal and drinking less than 210 mL ethanol per week. Subjects satisfying the entry criteria (138 of 1248 screened) were provided with detailed information about the aims and protocol of the project before giving signed consent, according to procedures established by the institutional human rights committee. They were then randomly allocated to one of seven groups before entering a 1-week baseline period before dietary intervention.

Volunteers received detailed dietary counseling about the diet plan and appropriate energy level to be followed for the duration of the study. During the subsequent 12-week intervention period, seven 24-hour food records were completed on randomly selected days and manually checked at each visit to ensure compliance with the dietary instructions.

Dietary Intervention

After the collection of baseline measurements, subjects entered a 12-week dietary intervention period in which five groups were assigned to diets providing 40% and two groups to diets providing 30% of total daily energy from fat (Fig 1). The five groups in the 40% fat category were then allocated to either a control group or a dietary-supplementation group with 6 or 12 daily 1.0-g fish-oil capsules (Lipitac, Reckitt & Colman Pharmaceuticals, Sydney, Australia), fish, or a combination of Lipitac and fish. The two groups consuming a 30% fat diet were treated either as a control or fish group, respectively. Fish in the form of frozen Greenland turbot fillets or canned sardines, tuna, and salmon was provided free of cost to participants in the relevant groups (groups 2, 4, and 7), who were instructed to eat one fish meal per day, prepared according to a variety of recipes incorporating all the selected fish, for the duration of the intervention.

Fish were derived from single batches to avoid seasonal variation in fatty acid composition. The fatty acid composition of fish fat and Lipitac is given in Table 1. The amount of fish was calculated to deliver approximately 1.3 g of eicosapentaenoic acid (EPA)/d, this

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Greenland turbot</th>
<th>Salmon</th>
<th>Tuna</th>
<th>Sardines</th>
<th>Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:0</td>
<td>5.50</td>
<td>4.52</td>
<td>5.46</td>
<td>4.63</td>
<td>5.89</td>
</tr>
<tr>
<td>14:1 ω5</td>
<td>0.13</td>
<td>0.13</td>
<td>0.13</td>
<td>0.24</td>
<td>0.16</td>
</tr>
<tr>
<td>15:0</td>
<td>0.28</td>
<td>1.06</td>
<td>0.48</td>
<td>0.35</td>
<td>0.45</td>
</tr>
<tr>
<td>16:0</td>
<td>13.10</td>
<td>19.09</td>
<td>17.18</td>
<td>15.54</td>
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</tr>
<tr>
<td>16:1 ω7</td>
<td>11.35</td>
<td>5.64</td>
<td>7.84</td>
<td>5.93</td>
<td>8.51</td>
</tr>
<tr>
<td>17:0</td>
<td>0.94</td>
<td>0.59</td>
<td>0.88</td>
<td>0.90</td>
<td>1.52</td>
</tr>
<tr>
<td>17:1 ω9</td>
<td>0.42</td>
<td>0.50</td>
<td>0.92</td>
<td>0.67</td>
<td>1.57</td>
</tr>
<tr>
<td>18:0</td>
<td>1.41</td>
<td>4.62</td>
<td>4.02</td>
<td>2.20</td>
<td>2.96</td>
</tr>
<tr>
<td>18:1 ω9</td>
<td>20.22</td>
<td>16.30</td>
<td>16.08</td>
<td>19.14</td>
<td>11.92</td>
</tr>
<tr>
<td>18:2 ω6</td>
<td>1.32</td>
<td>1.36</td>
<td>1.10</td>
<td>10.92</td>
<td>1.88</td>
</tr>
<tr>
<td>18:3 ω3</td>
<td>0.63</td>
<td>2.68</td>
<td>1.02</td>
<td>2.63</td>
<td>1.02</td>
</tr>
<tr>
<td>18:4 ω3</td>
<td>2.02</td>
<td>4.01</td>
<td>3.43</td>
<td>2.79</td>
<td>3.74</td>
</tr>
<tr>
<td>20:1 ω9</td>
<td>13.17</td>
<td>1.18</td>
<td>3.07</td>
<td>6.55</td>
<td>2.33</td>
</tr>
<tr>
<td>20:4 ω6</td>
<td>0.40</td>
<td>1.35</td>
<td>0.88</td>
<td>0.28</td>
<td>1.31</td>
</tr>
<tr>
<td>20:4 ω3</td>
<td>0.52</td>
<td>0.61</td>
<td>1.11</td>
<td>0.57</td>
<td>1.25</td>
</tr>
<tr>
<td>20:5 ω3</td>
<td>7.39</td>
<td>6.73</td>
<td>15.82</td>
<td>7.99</td>
<td>21.96</td>
</tr>
<tr>
<td>22:1 ω11</td>
<td>11.75</td>
<td>0.27</td>
<td>2.95</td>
<td>7.64</td>
<td>1.37</td>
</tr>
<tr>
<td>22:4 ω6</td>
<td>0.14</td>
<td>0.32</td>
<td>0.10</td>
<td>0.10</td>
<td>0.23</td>
</tr>
<tr>
<td>22:5 ω3</td>
<td>0.81</td>
<td>1.96</td>
<td>2.17</td>
<td>0.92</td>
<td>2.72</td>
</tr>
<tr>
<td>22:6 ω3</td>
<td>8.50</td>
<td>27.08</td>
<td>15.36</td>
<td>10.01</td>
<td>14.35</td>
</tr>
<tr>
<td>ω3/ω6</td>
<td>10.68</td>
<td>14.21</td>
<td>18.71</td>
<td>2.20</td>
<td>13.17</td>
</tr>
</tbody>
</table>

Fig 1. Schematic outline shows study protocol and group allocation. One capsule indicates 6 Lipitac capsules taken daily; two capsules indicate 12 capsules taken daily.
Measurements were taken twice during each of the
three consecutive 24-hour food records collected
before the dietary intervention period.

The diets were designed at six different energy levels,
from 6270 kJ (1500 kcal) to 11 495 kJ (2750 kcal) in
1045-kJ (250-kcal) increments, to accommodate individual
energy requirements from information obtained from
three consecutive 24-hour food records collected before the
dietary intervention period.

The diets supplying 40% fat had a polyunsaturated-
saturated ratio of less than 0.3, with 16% to 17% of daily
energy from protein and 43% to 44% from carbohydrates.
Fiber intake was 10 g per 4180 kJ and cholesterol
greater than 300 mg/d. The 30% fat diet had a poly-
saturated-saturated ratio of greater than 1, with protein
and carbohydrates providing 16% to 17% and 53% to
54% of energy, respectively.

Measurements
BP and HR were measured automatically with the
same Dinamap 1846 SX/P monitor7 for each subject.
Measurements were taken twice during each of the
screening and baseline periods, then every 4 weeks of
the intervention period including twice during the final
week. Subjects were rested for 10 minutes before BP
monitoring was begun. Supine measurements were
made at 2-minute intervals for 20 minutes and then
erect at 1-minute intervals for 5 minutes. Measurements
were recorded before venesection if this was scheduled
for the same visit. Subjects were weighed without shoes
and in light clothing on a calibrated beam balance.

Plasma glucose and 24-hour urinary sodium and
potassium concentrations were determined by standard
autoanalyzer methods, serum insulin levels by radioimmuno-
asay, and platelet phospholipid fatty acid composition
as previously reported.8 Total ω3 fatty acids measured included 20:5, 22:5, and 22:6, and ω6 fatty
acids measured included 18:2, 20:3, 20:4, and 22:4. Fish
fats were determined by similar methods in homogene-
ized flesh drained of oil (sardines) or brine (tuna and
salmon).

Analysis
Nutritional data obtained from diet records was an-
alyzed by computer using the NUTTAB® database.
Statistical analyses were performed with SPSS/PC using
analysis of variance or Mann-Whitney tests and by
stepwise multiple regression analyses as indicated. Sig-
nificance levels were modified for multiple comparisons
by the Bonferroni method. Values are reported as
means (SEM).

Results
Of the 138 subjects randomized, 120 completed the
study. Those who withdrew were unable either to main-
tain the schedule of laboratory visits or to comply with
the dietary requirements. Baseline characteristics for
the seven groups are shown in Table 2, confirming that
the groups were well matched for the selection vari-
ables. Analysis of the diet records and lifestyle ques-
tionnaires indicated no major changes in energy intake
or alterations in nutrient balance, alcohol drinking, or
physical activity during the intervention. Evidence of
adherence to the diet, obtained from diet records and
confirmed from platelet fatty acid composition, indi-
cated more than 95% compliance. It was found, how-
ever, that some subjects experienced considerable diffi-

TABLE 2. Baseline Characteristics of Study Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>BMI</th>
<th>SBP</th>
<th>DBP</th>
<th>Serum cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(y)</td>
<td>(kg/m²)</td>
<td>(mm Hg)</td>
<td>(mm Hg)</td>
<td>(mmol/L)</td>
</tr>
<tr>
<td>40% Fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=18)</td>
<td>45.4 (1.4)</td>
<td>27.8 (0.6)</td>
<td>135.8 (2.1)</td>
<td>84.7 (1.4)</td>
<td>6.2 (0.1)</td>
</tr>
<tr>
<td>Fish (n=17)</td>
<td>44.2 (1.7)</td>
<td>28.6 (0.6)</td>
<td>136.4 (2.1)</td>
<td>83.9 (1.2)</td>
<td>6.2 (0.1)</td>
</tr>
<tr>
<td>6 Lipitac capsules (n=17)</td>
<td>46.8 (1.2)</td>
<td>27.4 (0.5)</td>
<td>137.3 (2.6)</td>
<td>85.0 (1.8)</td>
<td>6.1 (0.2)</td>
</tr>
<tr>
<td>Fish+6 Lipitac capsules (n=17)</td>
<td>44.7 (1.5)</td>
<td>27.8 (0.5)</td>
<td>137.1 (1.7)</td>
<td>85.0 (1.5)</td>
<td>6.1 (0.1)</td>
</tr>
<tr>
<td>12 Lipitac capsules (n=16)</td>
<td>44.9 (1.9)</td>
<td>26.2 (0.7)</td>
<td>136.4 (2.0)</td>
<td>85.2 (1.3)</td>
<td>6.0 (0.2)</td>
</tr>
<tr>
<td>30% Fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (n=17)</td>
<td>48.3 (2.1)</td>
<td>26.8 (0.7)</td>
<td>136.4 (3.0)</td>
<td>84.9 (2.0)</td>
<td>6.0 (0.3)</td>
</tr>
<tr>
<td>Fish (n=18)</td>
<td>45.6 (1.6)</td>
<td>27.5 (0.6)</td>
<td>136.0 (1.7)</td>
<td>84.8 (1.1)</td>
<td>6.0 (0.1)</td>
</tr>
<tr>
<td>Total (n=120)</td>
<td>45.7 (0.6)</td>
<td>27.5 (0.2)</td>
<td>136.5 (0.8)</td>
<td>84.8 (0.6)</td>
<td>6.1 (0.1)</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are mean (SEM).

being equivalent to the quantity of EPA provided by 6
Lipitac capsules. Two levels of EPA supplementation,
1.3 and 2.6 g/d, the latter in the form of 6 Lipitac
capsules plus fish (group 4) or 12 Lipitac capsules
(group 5), were compared. Because of the variable
proportions of the other major ω3 fatty acid, docos-
ahexaenoic acid (DHA), in fish, there were small differ-
ences in total ω3 fats provided by each species. Subjects
were asked to eat either approximately 160 g/d of
Greenland turbot fillets, approximately 95 g/d of canned
sardines, approximately 90 g/d of canned tuna, or
approximately 90 g/d of canned salmon. This quantity of
fish provided approximately 3.5, 4.1, 3.2, and 3.8 g/d,
respectively, of total ω3 fatty acids. However, as the
menus were designed to include all fish, the average
daily intake of ω3 fats was likely to be similar. This was
confirmed by subsequent analyses of diet records.

Placebo capsules containing a combination of olive/
palm/safflower oils (1:4.5:4.5) and providing approxi-
mately the same ratio of saturated to monounsaturated
to polyunsaturated fatty acids as in the Lipitac capsules
(Table 1) were given to groups 1, 2, 6, and 7 as shown in
Fig 1. All groups were advised to reduce sodium intake
to less than 90 mmol/d by avoiding added salt and
known salty foods and by eating low-salt bread, marga-
rine, and butter.

Of the 138 subjects randomized, 120 completed the
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confirmed from platelet fatty acid composition, indi-
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Fig 2. Line graphs of supine systolic and diastolic blood pressures (BP) and heart rate show familiarization effect with BP during baseline period. Solid symbols, 40% fat diet groups; open symbols, 30% fat groups. One capsule indicates 6 Lipitac capsules taken daily; two capsules indicate 12 capsules taken daily.

culty coping with the recommended intake of canned salmon, and in these individuals it became necessary to reduce this from 180 to 90 g/d, halving the amount of EPA and total w3 fatty acids from this source to 0.65 and 3.8 g/d, respectively. However, the total w3 fat intake, which ranged from 3.2 to 4.1 g/d depending on the fish consumed (see "Methods"), remained comparable among all groups, as menus were designed to include all fish.

Blood Pressure, Heart Rate, Urinary Sodium and Potassium, Blood Glucose, and Insulin

Supine BP and HR recordings throughout the study for all seven groups are shown in Fig 2. Mean changes in supine and erect BP and HR, representing the difference between end of intervention levels (average of two measurements in weeks 15 and 16) and baseline levels (average of two measurements in week 4), and weight (difference between week 16 and week 4) are given in Table 3. There was no significant group effect on the changes in weight or supine or erect BP, although the average supine BP fall was greater in the 40% total fat, fish, or fish-oil groups compared with controls and in the two 30% fat groups. The average erect BP fall was also greater in the 40% total fat, fish, or fish-oil groups compared with controls and in the 30% fat fish group. A greater percentage of subjects in the low-fat fish group (group 7) experienced a fall in BP during the intervention. For this group, 14 of 18 subjects showed a fall in systolic supine (P < .01) and erect (P < .01) BP, and 12 of 18 experienced a reduction in diastolic supine and erect BP (P = NS), using the Sign Test. Supine HR increased in both control groups, in contrast to the fall in fish and Lipitac groups (Table 3). Similar differences between control and fish or Lipitac groups were seen for erect HR, although this was of borderline significance (P = .06). Adjustment for weight changes did not influence these results.

The changes in HR and BP (difference between the last intervention visit at week 16 and the first baseline visit at week 4) were highly correlated. For all groups combined, the change in HR was correlated with the change in supine (r = .83, P < .0001) and erect (r = .53, P < .0001) systolic BP and supine (r = .99, P < .0001) and erect (r = .55, P < .0001) diastolic BP.

At baseline, there were no significant differences between 24-hour urinary sodium or potassium excretions, blood glucose, or insulin concentration. For the groups combined, mean urinary sodium excretion was 157 (4.0) mmol/24 h, potassium was 77 (1.8) mmol/24 h, blood glucose was 5.3 (0.06) mmol/L, and insulin was 10.0 (0.6) mU/L. Changes in 24-hour urinary electrolytes (difference between week 16 and the average of two values in week 4) and blood glucose and insulin concentration (difference between week 16 and week 3) are shown in Table 4. There was a uniform reduction in urinary sodium excretion consistent with the dietary instructions. Urinary potassium excretion was more variable, with the largest increase occurring in the 30% fat control group, presumably related to a higher intake of fruit and vegetables. Blood glucose and insulin (Table 4) and the glucose-insulin ratio did not show a treatment effect.

Platelet Phospholipid Fatty Acids

The baseline composition of platelet phospholipids consisted of 26.82 ± 0.13% arachidonic acid (20:4 w6), 0.52 ± 0.03% EPA (20:5 w3), and 4.69 ± 0.10% DHA (22:6 w3). The changes in percentage fatty acid composition between baseline (week 4) and the end of intervention (week 16) for each of these fatty acids are shown in Fig 3. In each case, there was a highly significant group effect (P < .00001), reflecting the incorporation of w3 fatty acids and displacement of 20:4 w6.
Platelet Phospholipid ω3 and Fatty Acids

Relations Between Changes in Blood Pressure and in Platelet Phospholipid ω3 and ω6 Fatty Acids

For all groups combined, there were highly significant and positive correlations between the decrease in platelet ω6 fatty acids (largely 20:4 ω6) and the changes in supine (r=−.23, P=.007) and erect (r=−.26, P=.002) systolic BP and supine (r=−.19, P=.018) and erect (r=−.24, P=.005) diastolic BP. These correlations were negative and considerably weaker for the increase in ω3 fatty acids and reached significance for erect systolic (r=−.16, P=.044) and diastolic (r=−.16, P=.038) BP only.

Because the changes in ω3 and ω6 fatty acids were strongly interdependent, a factor based on a linear combination of ω3 and ω6 fatty acids (extracted by principal component analyses with varimax rotation) from 20:3 to 22:6 was determined that explained 59% of the variance related to changes in these fatty acids. The coefficients for the individual fatty acids were 20:3 ω6, 0.61; 20:4 ω6, 0.88; 20:5 ω3, −0.89; 22:4 ω6, 0.87; 22:5 ω3, −0.06; and 22:6 ω3, −0.79, with the ω3/ω6 factor=(0.61×Δ20:3)+(0.88×Δ20:4)−(0.89×Δ20:5)+(0.87×Δ22:4)−(0.06×Δ22:5)−(0.79×Δ22:6). As changes in urinary electrolytes were also highly correlated, factors were extracted for inclusion in regression analysis. Multiple regression was then used to model changes in systolic or diastolic BP, adjusting for the effect of weight changes and change in urinary electrolytes. There was a significant and independent effect of the ω3/ω6 factor on the change in supine and erect systolic and diastolic BP (Table 5) after adjustment for change in weight and urinary variables. In the case of supine systolic BP, the variables in the model accounted for approximately 20% of the variance, with change in BP as the dependent variable.

Although the change in plasma glucose was small, incorporating the change in plasma glucose concentration into the model demonstrated an effect, independent of changes in weight, urinary variables, and the ω3/ω6 factor, that was significant for the change in erect systolic BP (P=.0110, r²=.2179) and reached a significance level of less than .1 for the change in supine systolic BP (P=.0967, r²=.2243). This indicates an association between the fall in both BP and blood glucose concentration. No such relations were apparent for the changes in blood insulin concentration or in the glucose-insulin ratio.

There were similar significant relations, independent of change in weight, between the decrease in platelet ω6

TABLE 3. Changes in Blood Pressure, Heart Rate, and Weight From Baseline to End of Intervention in Study Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Heart rate (bpm)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Erect</td>
<td>Supine</td>
<td>Erect</td>
</tr>
<tr>
<td>40% Fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>−1.0 (1.2)</td>
<td>−0.9 (1.8)</td>
<td>0 (1)</td>
<td>−1.1 (1.3)</td>
</tr>
<tr>
<td>Fish</td>
<td>−3.4 (1.4)</td>
<td>−2.8 (2.0)</td>
<td>−2.3 (1.2)</td>
<td>−1.4 (1.4)</td>
</tr>
<tr>
<td>6 Lipitac capsules</td>
<td>−4.5 (1.4)</td>
<td>−3.9 (1.7)</td>
<td>−2.5 (1)</td>
<td>−2.1 (1.1)</td>
</tr>
<tr>
<td>Fish+6 Lipitac capsules</td>
<td>−2.8 (1.9)</td>
<td>−1.5 (1.5)</td>
<td>−2.4 (1.3)</td>
<td>−2.4 (1.5)</td>
</tr>
<tr>
<td>12 Lipitac capsules</td>
<td>−2.3 (1.1)</td>
<td>−5.3 (0.9)</td>
<td>−1.2 (0.9)</td>
<td>−2.5 (0.8)</td>
</tr>
<tr>
<td>30% Fat</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>−3.2 (2.2)</td>
<td>−3.0 (2.2)</td>
<td>−3.4 (1.3)</td>
<td>−0.9 (1.1)</td>
</tr>
<tr>
<td>Fish</td>
<td>−4.7 (1.6)</td>
<td>−6.5 (2.1)</td>
<td>−3.6 (1.5)</td>
<td>−3.6 (1.4)</td>
</tr>
</tbody>
</table>

bpm, Beats per minute. Values are mean (SEM).

*Significant group effect by analysis of variance (P<.01).
†Borderline significant effect by analysis of variance (P=.06).

in those subjects consuming fish and Lipitac capsules. The greater reduction in 20:4 ω6 and increase in 22:6 ω3 in group 2 compared with group 3 is probably attributable to the higher content of 22:6 ω3 in fish.

Values are mean (SEM).

*Significant group effect by analysis of variance (P=.052).

TABLE 4. Changes in Sodium and Potassium Excretions and Blood Glucose and Insulin Concentration Between End of Intervention and Baseline Measurements in Study Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>24-Hour urine (mmol/24 h)</th>
<th>Blood Glucose (mmol/L)</th>
<th>Insulin (mU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na*</td>
<td>K**</td>
<td></td>
</tr>
<tr>
<td>40% Fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>−67 (13)</td>
<td>−2 (8)</td>
<td>0.2 (0.2)</td>
</tr>
<tr>
<td>Fish</td>
<td>−90 (16)</td>
<td>0 (7)</td>
<td>0.2 (0.1)</td>
</tr>
<tr>
<td>6 Lipitac capsules</td>
<td>−94 (11)</td>
<td>0.7 (13)</td>
<td>0.3 (0.2)</td>
</tr>
<tr>
<td>Fish+6 Lipitac capsules</td>
<td>−76 (10)</td>
<td>15 (8)</td>
<td>0.3 (0.2)</td>
</tr>
<tr>
<td>12 Lipitac capsules</td>
<td>−77 (14)</td>
<td>−10 (8)</td>
<td>0 (0.1)</td>
</tr>
<tr>
<td>30% Fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>−98 (16)</td>
<td>30 (9)</td>
<td>0 (0.1)</td>
</tr>
<tr>
<td>Fish</td>
<td>−100 (13)</td>
<td>14 (9)</td>
<td>−0.1 (0.1)</td>
</tr>
</tbody>
</table>

Values are mean (SEM).

*Significant group effect by analysis of variance (P=.052).
Bar graphs show changes in percentage of 20:4 (ω6), 20:5 (ω3), and 22:6 (ω3) in platelet phospholipids after dietary intervention in the seven groups. Values are mean±SEM. Analysis of variance shows significant group effect (P<.00001). *P<.01, **P<.001 for difference between groups 2 and 3. Shaded bars, 40% fat; hatched bars, 30% fat. One capsule indicates 6 Lipitac capsules taken daily; two capsules indicate 12 capsules taken daily.

fatty acids and the fall in supine HR (P=.0001, \(r^2=.1188\)) and erect HR (P=.002, \(r^2=.1030\)), as well as between the increase in ω3 fatty acids and fall in HR (P=.014, \(r^2=.0513\) and P=.021, \(r^2=.0702\) for supine and erect HR, respectively). Using the factor for change in ω3/ω6, regression analyses confirmed significant relations with the changes in supine (P=.00001) and erect (P=.0004) HR.

Figs 4 and 5 illustrate the relation between changes in supine and erect BP and HR according to tertiles of change in ω3 and ω6 fatty acids, respectively, for the entire group.

**Discussion**

This randomized, controlled study failed to demonstrate a specific group hypotensive effect of fish or fish-oil supplements with high- or low-fat diets in volunteers with moderate cardiovascular risks and BP in the higher normal range. However, for the entire population studied, there were highly significant relations between the fall in BP during dietary intervention and the decrease in ω6 and, to a lesser degree, the increase in ω3 fatty acids in platelet phospholipids. The latter finding is in keeping with that reported by Bonaa and colleagues for changes in plasma phospholipid ω3 fatty acids and blood pressure in subjects fed fish oil. The stronger relation between the BP fall and the displacement of ω6 rather than the incorporation of ω3 fatty acids in our study may reflect the abundance of ω6 fatty acids in platelet phospholipids and hence greater precision in measurement.

The higher percentage of 22:6 ω3 and corresponding lower percentage of 20:4 ω6 in platelet phospholipids in the fish groups, as opposed to the Lipitac groups, reflects the greater proportion of 22:6 ω3 in fish. The lower percentage of 20:5 ω3 in the Lipitac group receiving an equivalent amount of EPA compared with those eating fish is consistent with evidence that some of this fatty acid is derived from 22:6 ω3. Because the changes in ω6 and ω3 fatty acids are closely linked, applying a factor that takes into account changes in both fatty acids in the regression analyses improved the relation, with the changes in BP independent of the changes in weight and urinary sodium and potassium.

Mechanisms whereby these alterations in ω3 and ω6 fatty acids lower BP have been discussed in detail in several recent reviews. The evidence to date suggests that these mechanisms may in part involve impairment of platelet and possibly vascular synthesis of the

**Table 5. Regression Models Examining Relations Between Changes in Blood Pressure and Changes in Weight, and in Factors Incorporating Changes in Urinary Na+ and K+ and Platelet ω3 and ω6 Content**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change in supine SBP</th>
<th>Change in supine DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\beta)</td>
<td>(P)</td>
</tr>
<tr>
<td>ΔUrinary Na+/K+ factor</td>
<td>.295</td>
<td>.0013</td>
</tr>
<tr>
<td>ΔWeight</td>
<td>.183</td>
<td>.0434</td>
</tr>
<tr>
<td>Δω3 and ω6 factor</td>
<td>.210</td>
<td>.0150</td>
</tr>
<tr>
<td>(r^2=.2051)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Change in erect SBP</th>
<th>Change in erect DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\beta)</td>
<td>(P)</td>
</tr>
<tr>
<td>ΔUrinary Na+/K+ factor</td>
<td>.227</td>
<td>.0144</td>
</tr>
<tr>
<td>ΔWeight</td>
<td>.179</td>
<td>.0529</td>
</tr>
<tr>
<td>Δω3 and ω6 factor</td>
<td>.242</td>
<td>.0061</td>
</tr>
<tr>
<td>(r^2=.1714)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure.
vasoconstrictor thromboxane A₂ or its endoperoxide precursors, enhanced endothelium-dependent relaxation,⁵,¹⁴ or reduced vascular reactivity to norepinephrine.⁵,¹⁶ Supplementation of ω3 fatty acids in humans, however, has shown to have no effect on catecholamine excretion in healthy males⁷ or the BP increases either to psychological stress in mild essential hypertensive patients¹⁸ or to cold pressor testing in hypertensive subjects.¹⁹ A recent study has shown that fish oils dose-dependently suppress vascular reactivity in vivo in humans by an indomethacin-sensitive mechanism.²⁰ In this latter study, responses to local intra-arterial infusions of norepinephrine and angiotensin II were examined using forearm venous occlusion plethysmography and found to be reduced after supplementation with fish oil for 28 days. Furthermore, the suppressive effects of the fish oil were no longer apparent after 2 days of indomethacin treatment.

The lack of a BP-lowering effect of fish or fish oil providing approximately 3 to 4 g of ω3 fats per day is supported by the study of Knapp and FitzGerald,²¹ in which 15 g but not 3 g of ω3 fats daily for 4 weeks lowered BP in men with mild essential hypertension. A similar but larger study in essential hypertension using 6 g of ω3 fats daily for 10 weeks also reported a significant fall in BP, which was mainly confined to those subjects eating fewer than three fish meals a week. This confirmed an earlier preliminary report in which 6 g/d of ω3 fats for 6 weeks lowered systolic BP in untreated hypertensive subjects.²² In a recently published study,⁶ elderly normotensive subjects given 5 g of ω3 fats for 4 weeks showed a BP fall only when placed on a lowsodium diet that matched the reduction in urinary sodium achieved in our subjects. However, a similar fall in BP, particularly systolic BP, was seen in the sodium-depleted control group receiving sunflower oil.⁶ The same laboratory also demonstrated a fall in systolic BP in normotensive men given 3.4 g/d of ω3 fats for 6 weeks who were not sodium restricted.²³ A lower dose of ω3 fatty acids, 2.5 g/d for 5 weeks, also appeared to be effective in a placebo-controlled study in normotensive subjects with no reported change in sodium balance.²⁴ Similarly, 1.0 to 2.0 g/d of ω3 fatty acids as fish oil, given for 12 weeks in a linoleic acid–controlled crossover trial, lowered BP in mildly hypertensive subjects, although possible changes in sodium intake and other dietary factors were not addressed.²⁵ Considering these results, it seems unlikely that the absence of a statistically significant hypotensive effect of ω3 fats in our study can be explained in terms of the quantity of ω3 fats administered, concurrent sodium status, duration of intervention, or the presence of unequivocal hypertension. The total fat content of the diet also appeared to be unimportant, and only subjects eating one or less than one fish meal a week were included to optimize detection of a BP effect. Negative results in normotensive subjects have also appeared from other centers using up to 6 g of ω3 fats daily for 12 weeks²⁶ or 4.7 g/d as mackerel paste for 6 weeks.²⁷
Inadequate power to detect a BP fall, over and above that attributable to familiarization or regression to the mean, due to small sample size may be why a specific group effect of \( \omega_3 \) fats was not detected. Considerably smaller group sizes were used by Knapp and FitzGerald, but in their study, mean BP in the control groups did not fall relative to baseline, presumably because ambulatory BP was measured, which avoids the familiarization effect. Small sample size also was not an issue in the TOHP trial, in which 175 subjects with high normal BP were given 3.0 g \( \omega_3 \) fats daily for 6 months without change in BP.

Of considerable interest was the finding that HR decreased uniformly in the intervention groups and that for the entire group changes in HR were significantly related to the decrease in \( \omega_6 \) and increase in \( \omega_3 \) fatty acids in platelet phospholipids. This was less evident in erect than in supine HR measurements, possibly because of the overriding influence of compensating reflexes activated when standing up. Conceivably, incorporation of \( \omega_3 \) fatty acids into myocardial cells results in metabolic and functional changes allied to those implicated in the antiarrhythmic effect of fish oils in animal experiments.

In summary, although this study did not show a significant dietary group effect of \( \omega_3 \) fats, either as fish or fish oil or in the presence of a low or high saturated fat diet, on BP and HR in men with high normal BP, it has demonstrated a significant relation between the fall in BP and the changes in platelet phospholipid \( \omega_3 \) and \( \omega_6 \) fatty acid incorporation when the data from \( \omega_3 \) fatty acid-supplemented and control groups were combined. This relation was independent of changes in weight, urinary sodium and potassium excretions, and blood glucose concentration. The reduction in HR in the \( \omega_3 \) intervention groups was also related to the increase in \( \omega_3 \) and decrease in \( \omega_6 \) in platelet fatty acids. It is suggested that similar changes in phospholipid fatty acid composition at the vascular and myocardial levels may provide a mechanism underlying these observations.

Acknowledgments

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Effects on blood pressure of omega 3 fats in subjects at increased risk of cardiovascular disease.
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