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# Can n-3 PUFA reduce cardiac arrhythmias? Results of a clinical trial

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**Abstract**

Dietary n-3 polyunsaturated fatty acids (PUFA) derived from fatty fish or fish oil may reduce the incidence of lethal myocardial infarction and sudden cardiac death. This might be due to a prevention of fatal cardiac arrhythmias. So far, however, only few clinical data are available being adequate to define indications for an antiarrhythmic treatment with n-3 PUFA.

In a randomized, double-blind, placebo-controlled study 65 patients with cardiac arrhythmias without coronary heart disease or heart failure were subdivided into 2 groups. One group ($n = 33$) was supplemented with encapsulated fish oil (3 g/day, equivalent to 1 g/day of n-3 PUFA) over 6 months. The other group ($n = 32$) was given 3 g/day of olive oil as placebo. In the fish oil group a decrease of serum triglycerides, total cholesterol, LDL cholesterol, plasma free fatty acids and thromboxane $B_2$ as well as an increase of HDL cholesterol were observed. Moreover, a reduced incidence of atrial and ventricular premature complexes, couplets and triplets were documented. Accordingly, higher grades of Lown's classification switched to lower grades at the end of the dietary period. No changes were seen in the placebo group.

The data indicate an antiarrhythmic action of n-3 PUFA under conditions of clinical practice which might help to explain the reduced incidence of fatal myocardial infarction and sudden cardiac death in cohorts on a fish-rich diet or supplemented with n-3 PUFA. Further studies elucidating the possible link between the reduced incidence of cardiac arrhythmias and sudden cardiac death by dietary intake of n-3 PUFA are warranted.


## 1. Introduction

There is increasing evidence from epidemiological and clinical studies that n-3 PUFA exert a beneficial effect on several risk factors of coronary heart disease (CHD) and, accordingly, might be important for primary and secondary prevention [1–4]. A reduced incidence of fatal myocardial infarction by nearly 50% in populations on a habitual diet rich in fatty fish as well as a decreased rate of lethal reinfarction by 30% despite unchanged plasma cholesterol levels after fish diet or fish-oil supplementation [5,6] were assumed to be due to diminished coronary thrombosis and lethal cardiac arrhythmias. Moreover, recent epidemiological results indicate a reduced incidence of sudden cardiac death by a diet rich in n-3 PUFA [7–9]. Sudden death is often found in patients with CHD but will even occur if signs of CHD are absent. It might be predicted by recording cardiac arrhythmias even in patients with asymptomatic or mildly symptomatic ventricular premature complexes (VPC).

In numerous animal experiments an antiarrhythmic action of n-3 PUFA was found [10–13]. However, only few clinical data are available which suggest an evidence-based recommendation of n-3 PUFA to reduce ventricular arrhythmias in clinical practice [14–17]. We, therefore, designed a study to examine the antiarrhythmic effect of encapsulated fish oil on cardiac arrhythmias in patients without signs of CHD and heart failure.

## 2. Materials and methods

### 2.1. Patients

A total of 65 patients (32 male, 33 female) with cardiac arrhythmias without signs of CHD and heart failure were randomly allocated to 2 subgroups. The first group ($n = 33$) was supplemented with 3 g/day of fish oil ($3 \times 2$ or $2 \times 3$ capsules a 0.5 g) over 6 months.

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The other group ($n = 32$) was given 3 g/day of olive oil ($3 \times 2$ capsules or $2 \times 3$ capsules a 0.5 g) as placebo.

The mean age of the fish oil group (17 male, 16 female) was $45 \pm 8$ years (mean $\pm$ SD), the body height being $167 \pm 10$ cm and body weight $74 \pm 10$ kg. The mean age in the placebo group (15 male, 17 female) was $42 \pm 9$ years, body height $169 \pm 9$ cm and body weight $74 \pm 11$ kg.

The patients complained about palpitation, irregular heart beats and/or episodes of tachycardia irrespective of physical activities for at least 2 months. Before entry into the study CHD and heart failure were excluded by electrocardiography (ECG) in rest and after exercise as well as echocardiography (L/S 2500, Picker International). Patients were excluded if their fractional shortening was estimated to be $<25\%$. No episodes of angina pectoris or dyspnoe were reported from the subjects. Their ECG revealed no signs of CHD besides isolated atrial (APC) and VPC including couplets and triplets before entry into the trial. For ethical reasons only patients with moderate to low-grade arrhythmias in the absence of CHD and heart failure were studied.

The diagnoses of the patients were as follows: neurodystonia ($n = 21$), interatrial septal defect ($n = 2$), diffuse goitre ($n = 7$), latent hyperthyreosis ($n = 4$), shoulder–hand syndrome ($n = 10$), lumbalgia ($n = 9$), luxations ($n = 6$), migraine ($n = 6$), tension headache ($n = 8$), psoriasis ($n = 7$), eczema ($n = 11$), urinary tract infection ($n = 7$), hemorrhoidal complaints ($n = 5$)-partly in combination. The patients did not receive any long-term treatment. Transient intakes of antalgics and NSAR, respectively, were allowed. All participants were non-smokers. Patients with serum cholesterol above 240 mg/dl, blood pressure above 135/85 mm Hg and diabetes mellitus were excluded. All patients gave their informed consent prior to the study. The procedures followed were in accord with the Helsinki Declaration of 1975 as revised in 1983.

During the study no heart attacks, atrial fibrillation or other arrhythmias were observed. No unwanted effects were registered. Trivial diseases or accidents as well as short vacations were no reason to interrupt or stop the participation in the study.

### 2.2. Diet

Prior to the study the patients were interviewed on their habitual fish consumption. The fish intake was poor not exceeding one fish dish per month. Before entry into the study the energy intake was 9120–9450 kJ/day with a ratio of carbohydrates:fat:protein as 40:40:20 without changing during the trial. After subdivision the energy intake was 9060–9480 kJ/day with a ratio of carbohydrates:fat:protein as 41:39:20 in the fish oil group and 9120–9510 kJ/day with a ratio of carbohydrates:fat:protein as 40:41:19 in the placebo group without changes during the trial. The diet was supervised by a dietician and by telephone advice. The patients' compliance was controlled by consulting, weight control and estimation of the fatty acid pattern of serum triglycerides (Table 1).

The individuals of the fish oil group were given 3 g/day of encapsulated fish oil ($3 \times 2$ or $2 \times 3$ capsules a 0.5 g per day; 18% eicosapentaenoic acid (EPA), 12% docosahexaenoic acid (DHA), Ameu® provided by Omega Pharma GmbH, Berlin, Germany), adequate to 1 g/day of long-chain n-3 PUFA, over 6 months. Thereafter, the subjects were followed over a further period of 6 months (control). The participants of the placebo group were given 3 g/day of olive oil ($3 \times 2$ or $2 \times 3$ capsules a 0.5 g per day) over 6 months. Thereafter, the patients switched to their diet prior to the study also being followed over a period of 6 months (control).

### 2.3. Weight and blood pressure measurement

In all individuals before the trial, after 6 months (at the end of the dietary period) and after 12 months (control) body weight and blood pressure were measured in the morning after an overnight fasting (at least 12 h). Blood pressure was recorded in triplicate by the same observer using the same mercury sphygmomanometer with a standard cuff ($13 \times 53$ cm) placed about the midpoint of the left upper arm in sitting position. Diastolic blood pressure was recorded at the disappearance of Korotkoff sounds (phase 5).

Table 1
Selected n-6 and n-3 PUFA of serum triglycerides before and after diets supplemented with fish oil or olive oil (placebo)

| Fatty acids (%) | Placebo | Fish oil | | |
|---|---|---|---|---|
| | | Before | After diet (6 months) | Control (6 months later) |
| LA | $12.8 \pm 3.1$ | $13.1 \pm 2.9^{*}$ | $11.0 \pm 2.5^{*}$ | $12.9 \pm 3.3$ |
| AA | $1.6 \pm 0.6$ | $1.4 \pm 0.4$ | $1.5 \pm 0.7$ | $1.3 \pm 0.8$ |
| EPA | $0.4 \pm 0.3$ | $0.3 \pm 0.2^{**}$ | $1.4 \pm 0.6^{**}$ | $0.5 \pm 0.4$ |
| DHA | $0.6 \pm 0.5$ | $0.5 \pm 0.5^{**}$ | $4.3 \pm 1.2^{**}$ | $0.9 \pm 0.5$ |

LA indicates linoleic acid (n-6); AA, arachidonic acid (n-6); EPA, eicosapentaenoic acid (n-3) and DHA, docosahexaenoic acid (n-3). Data are expressed as mean $\pm$ SD. *Significance between before and after the diet and control, respectively, $P<0.05$; **$P<0.01$. The data of the placebo group at 6 and 12 months are not demonstrated.

### 2.4. Blood specimen collections

Thereafter, an indwelling catheter was inserted in an antecubital vein. Blood was withdrawn and taken in tubes for the estimation of serum lipids, lipoproteins and the fatty acid pattern of serum triglycerides. The samples were centrifuged immediately, portioned into tubes and analyzed on the same day. One hour later, again, blood was withdrawn for the estimation of plasma free fatty acids (FFA) and thromboxane $B_2$ ($TXB_2$) (see below) and stored at $-70^{\circ}C$.

### 2.5. Serum lipids and lipoproteins

Triglycerides and cholesterol concentrations were measured in serum by using commercially available enzymatic colorimetric kits (Boehringer Mannheim, Germany). HDL cholesterol was estimated after precipitating lipoproteins with polyethylene glycol 6000. LDL cholesterol was calculated from the values obtained for the total cholesterol, HDL cholesterol and triglycerides of each individual by using Friedewald's formula [18].

### 2.6. Fatty acid pattern of serum triglycerides

Serum lipids were separated by thin-layer chromatography on silica gel G 60 (Merck, Darmstadt, Germany). The plates were developed in *n*-hexane/diethylether/acetic acid (73:25:2, v/v/v). The lipid fractions were visualized under UV-light after spraying the plates with a solution of 0.1% dichlorofluorescein in ethanol. The triglyceride zones were scraped directly into glass tubes. The esterification was achieved by 0.5 M sodium methylate at room temperature. After addition of 0.5 M hydrochloric acid the methylesters were extracted with *n*-hexane and evaporated under nitrogen. The methylated fatty acids in hexane solution were directly injected into a gaschromatograph (Varian GC 3600, USA) at an 2.2 m × 1/8 inch column with 15% diethylene-glycol succinate (Supelco, USA) on Chromosorb W-AW (Serva, Germany) isothermal at 190°C using a flame ionisation detector. The component peaks were identified by reference to the retention time of authentic standards (Applied Science Laboratories, State College, USA). The relative proportion of each fatty acid in the fatty acid pattern was expressed as percentage of the sum of fatty acids resolved. The method has been published previously in detail [19].

### 2.7. Plasma FFA and $TXB_2$

After thawing plasma FFA were estimated according to the method of Duncombe [20]. The concentration of $TXB_2$, the stable metabolite of $TXA_2$, was measured in the platelet-poor plasma after centrifugation at $150 \times g$ for 10 min at room temperature followed by centrifugation at $2000 \times g$ for 15 min at room temperature [21] using an enzyme immunoassay method with commercially available kits (Cayman Chemical Company, Ann Arbor, USA).

### 2.8. ECG analysis

One hour after the second blood sampling an ambulatory 24-h Holter recording was obtained in each patient at the beginning of the trial, after 6 and 12 months using a Sherpa 2 for recording and a Pathfinder 700 (Reynolds Medical Ltd., Hertford, UK) for analyses. Recordings were printed in full length and controlled by a blinded experienced cardiologist. There were no speed errors in the recordings. The following variables were analyzed: QRS complexes (*n* per 24 h), APC and VPC (*n* per 24 h), couplets and triplets as well as assignment to Lown's grading system [22].

### 2.9. Statistical analysis

Results are given as mean and standard deviation (SD). Statistical analyses were performed by matched-pair *t*-test within one group comparing the values before the diet and at the end of the dietary period and control 6 months later. The level of significance was accepted as $P<0.05$ and $P<0.01$, respectively, being adjusted to Bonferroni modification.

## 3. Results

Selected n-6 and n-3 PUFA of serum triglycerides being estimated to verify the patients' compliance are shown in Table 1. In the fish oil group EPA and DHA were significantly increased whereas linoleic acid (LA) was decreased at the end of the dietary period. The values returned to the initial level 6 months after finishing the fish-oil supplementation (control). In the placebo group except a slight increase of oleic acid the values remained unchanged (not demonstrated).

Biochemical data and blood pressure are demonstrated in Table 2. Serum triglycerides, total and LDL cholesterol, plasma FFA and $TXB_2$ were significantly decreased whereas HDL cholesterol appeared increased after 6 months of fish-oil supplementation. All values, thereafter, reached the initial level 6 months after finishing the supplementation (control). Blood pressure remained unchanged. In the placebo group all parameters persisted on the level prior to the study.

Table 3 shows the 24-h Holter recordings before and after fish-oil supplementation. The incidence of QRS complexes per 24 h was only slightly reduced whereas the incidence of APC (−46.9%), VPC (−67.8%) and couplets (−71.8%) was significantly diminished. Triplets

Table 2
Serum lipids, lipoproteins, plasma FFA and $TXB_2$ and blood pressure before and after diets supplemented with fish oil or olive oil (placebo)

| | Before | After diet (6 months) | Control (6 months later) |
|---|---|---|---|
| Fish oil group ($n = 33$) | | | |
| Cholesterol (mg/dl) | 211±23* | 191±15* | 207±12 |
| LDL cholesterol (mg/dl) | 123±10* | 108±12* | 122±11 |
| HDL cholesterol (mg/dl) | 45±8* | 50±8 | 46±9 |
| Triglycerides (mg/dl) | 174±27** | 122±16** | 175±26 |
| FFA (μmol/l) | 476±232** | 109±87** | 484±153 |
| $TXB_2$ (pmol/l) | 161±73** | 71±25** | 163±65 |
| Systolic blood pressure (mmHg) | 129±6 | 127±8 | 130±7 |
| Diastolic blood pressure (mmHg) | 81±4 | 80±5 | 79±6 |
| Olive oil group ($n = 32$) | | | |
| Cholesterol (mg/dl) | 214±25 | 216±22 | 209±18 |
| LDL cholesterol (mg/dl) | 119±13 | 121±14 | 118±13 |
| HDL cholesterol (mg/dl) | 46±11 | 47±10 | 44±9 |
| Triglycerides (mg/dl) | 181±16 | 175±14 | 176±17 |
| FFA (μmol/l) | 454±170 | 438±159 | 465±168 |
| $TXB_2$ (pmol/l) | 168±82 | 179±63 | 181±72 |
| Systolic blood pressure (mmHg) | 131±5 | 130±6 | 129±5 |
| Diastolic blood pressure (mmHg) | 80±4 | 78±5 | 79±6 |

Data are expressed as mean±SD. *$P<0.05$, **$P<0.01$.

Table 3
24-h Holter recordings before and after diets supplemented with fish oil or olive oil (placebo)

| | Before | after diet (6 months) | Control (6 months later) |
|---|---|---|---|
| Fish oil group ($n = 33$) | | | |
| QRS complexes ($n$/24 h) | 101,458±9455 | 93,729±8114 | 103,508±8713 |
| APC ($n$/24 h) | 5112±835* | 2714±656* | 5091±717 |
| VPC ($n$/24 h) | 214±76* | 69±16* | 198±50 |
| Couplets ($n$/24 h) | 39±13* | 11±7* | 32±9 |
| Triplets ($n$/24 h) | 7±3 | — | 6±4 |
| Olive oil group ($n = 32$) | | | |
| QRS complexes ($n$/24 h) | 103,515±10,876 | 105,412±9953 | 106,709±9877 |
| APC ($n$/24 h) | 4988±759 | 5113±684 | 5017±705 |
| VPC ($n$/24 h) | 181±75 | 169±82 | 175±79 |
| Couplets ($n$/24 h) | 42±17 | 47±15 | 41±18 |
| Triplets ($n$/24 h) | 8±4 | 9±5 | 8±5 |

Data are expressed as mean±SD.
QRS complexes correspond to heart beats per 24 h, APC indicates atrial premature complexes.
VPC indicates ventricular premature complexes. *$P<0.01$. Couplets are 2 coupled VPC; triplets are salvos of 3 VPC.

were entirely disappeared. The values returned to their initial level 6 months later (control). As an instance of the antiarrhythmic action the 24-h Holter recordings from an individual of the fish oil group are demonstrated in the Fig. 1. Other arrhythmias like atrial flutter or fibrillation and ventricular tachycardia were not observed. Do drug treatment was necessary. In the placebo group the variables remained unchanged.

From Table 4 the incidence of individuals subdivided according to the grading system of Lown and Wolf [22] can be seen. The subjects with more severe ventricular arrhythmias (grades 3 and 4a) were markedly reduced whereas the low-grade ventricular arrhythmias (grades 0, 1 and 2) were increased at the end of the dietary

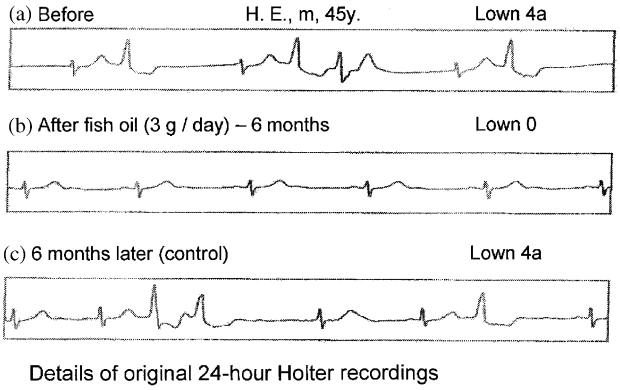


Fig. 1. Example of the antiarrhythmic action of fish oil.

Table 4
Grades of ventricular arrhythmias before and after diets supplemented with fish oil or olive oil (placebo)

| Grade | Before | After diet (6 months) | Control (6 months later) |
|---|---|---|---|
| Fish oil group ($n = 33$) | | | |
| 0 | — | 2 | 1 |
| 1 | 2 | 7 | 3 |
| 2 | 5 | 15 | 6 |
| 3 | 18 | 6 | 17 |
| 4a | 8 | 3 | 6 |
| Olive oil group ($n = 32$) | | | |
| 0 | - | - | - |
| 1 | 1 | - | 2 |
| 2 | 6 | 7 | 8 |
| 3 | 19 | 18 | 17 |
| 4a | 6 | 7 | 5 |

Grading system according to Lown and Wolf [22].

period in the fish oil group but remained unchanged in the placebo group. The initial distribution within the grading system was reached 6 months after finishing the fish-oil supplementation (control). No drop outs were registered.

## 4. Discussion

Numerous epidemiological, clinical and experimental data indicate a beneficial effect of dietary n-3 PUFA on the risk of CHD and sudden cardiac death [1–17]. The reduced incidence of fatal reinfarction [5,6] despite unchanged plasma cholesterol levels and of sudden cardiac death [7–10] suggest diminished ventricular arrhythmias in populations ingesting a habitual diet rich in fatty fish or supplemented with encapsulated fish oil. Based on recent epidemiological data the reduction of cardiac arrhythmias was discussed as a possible cause of reinfarction [5] and sudden cardiac death [7–9]. However, cardiac arrhythmias have not been recorded within the epidemiological studies mentioned above. Thus, evidence-based data which evaluate the causal role of ventricular arrhythmias for reinfarction and sudden cardiac death are not available. Moreover, there is only sparse information that directly shows an antiarrhythmic action of n-3 PUFA in humans. Therefore, it seems logical to explore the influence of n-3 PUFA on cardiac arrhythmias under clinical conditions.

In a recent study a reduced incidence of APC and VPC after a diet rich in fatty fish (3 cans/week of mackerel fillet, equivalent to nearly 1 g/day of n-3 PUFA, over 4 months) was found [17]. In view of those results we were encouraged to design a further study based on a diet supplemented with encapsulated fish oil providing likewise 1 g/day of n-3 PUFA.

The decrease of serum triglycerides, total and LDL cholesterol as well as an increase of HDL cholesterol is a common finding after dietary intake of n-3 PUFA [23,24] and will not be discussed in detail. The lacking reduction of blood pressure corresponds to literature data indicating that only elevated blood pressure is depressed by n-3 PUFA normal blood pressure remaining unchanged [24,25].

Because of their extreme variability and short biological half-life time FFA are difficult to measure and to interprete in clinical trials. Consequently, strictly standardized conditions are needed to avoid misinterpretation. Therefore, in order to eliminate stress response by venipuncture in our study venous blood was withdrawn 1 h after insertion of an indwelling catheter for estimation of plasma FFA and $TXB_2$. Possibly, methodical difficulties are the reason why the action of n-3 PUFA on FFA is widely ignored, although as early as 1964 the later Nobel prize winner Bergström (1982) had described a depression of catecholamine-induced lipolysis of prostaglandins [26]. By the way, a decrease of FFA jointly with glucose being a substrate for triglyceride formation in the liver was also discussed as a contribution to the established triglyceride-lowering action of n-3 PUFA [27]. Recently, the level of circulating FFA has been interpreted as an independent risk factor for sudden cardiac death in the population concluding that a decrease of FFA level might be a target for its prevention [28]. Immediately after myocardial infarction FFA are released from the hydrolysis of membrane phospholipids resulting in a calcium overload and other reactions in the myocardial cells [29,30]. The increase of FFA predisposes to ventricular arrhythmias [29,30] The type of FFA released determines the arrhythmic response of the myocardium [11]. The supply of n-3 PUFA in cardiomyocyte membrane is assumed to be essential for their antiarrhythmic action so that they are a retrievable reservoir for release as free acids to prevent arrhythmias following myocardial ischemia [10–13]. It can be assumed that certain individual FFA are more important than FFA as a whole. Indeed, it has been shown that EPA and DHA exert an antiarrhythmic action as free acids and not in phospholipids [31]. The mechanisms involved have been summarized by Nair et al. [11]. They can help to explain our results and recent epidemiological data, which emphasize the reduced rate of sudden cardiac death in populations on a diet rich in n-3 PUFA.

An additional aspect might be the depression of plasma $TXB_2$, measured as the stable metabolite of $TXA_2$, after fish-oil supplementation in our study. This is in agreement with a preceding paper describing a decrease of plasma $TXB_2$ associated with a reduced incidence of APC and VPC by a fish-rich diet providing likewise about 1 g/day of n-3 PUFA [17]. Obviously, it can be neglected that n-3 PUFA are supplied in form of

fatty fish or encapsulated fish oil (or in combination of both). The decrease of plasma $TXB_2$ induced by dietary n-3 PUFA might be paralleled by reduced myocardial $TXA_2$, a potent proarrhythmic substance [13]. Experimental data indicate a causal role of $TXA_2$ for sudden death [11]. Ventricular arrhythmias can be provoked dependent on the relation of $TXA_2$ and prostaglandin $I_2$ ($PGI_2$). $TXA_2$ was found to be released as an early response to occlusion of coronary arteries while $PGI_2$ was released after the onset of ischemia [32]. From these experiments it was postulated that an increase in the $PGI_2/TXA_2$ balance may be cardioprotective suggesting that $PGI_2$ predominates as an endogenous antiarrhythmic agent. This was confirmed by an inhibitory action of n-3 PUFA on thromboxane synthetase [33]. A decrease of $TXA_2$ and a concomitant increase of $PGI_2$ and $PGI_3$ after dietary n-3 PUFA has been described also in humans [34]. Consequently, reduced plasma $TXB_2$, the stable metabolite of $TXA_2$, might contribute to prevent cardiac arrhythmias. This may be important especially in coronary arteries already damaged by sclerotic lesions.

The results of our study confirm the data of a preceding trial providing 1 g/day of n-3 PUFA with fatty fish [17]. By encapsulated fish oil (1 g/day) over 6 months the reduction of APC (−47%) and VPC (−68%) was even more pronounced as compared with the fish diet over 4 months (APC −46% and VPC −53%, respectively). Despite an equal daily dose of n-3 PUFA this might be due to the higher total amount of n-3 PUFA after 6 months of fish-oil supplementation (180 g versus 120 g after fish diet over 4 months). This speculation is based on the assumption that n-3 PUFA accumulate in membrane phospholipids being a reservoir for release of n-3 PUFA as free fatty acids for supply of intracellular eicosanoid formation. The similar magnitude of reduced cardiac arrhythmias in our both studies is notable because the patients taking encapsulated fish oil over 6 months in the study presented were a low-risk group while the patients of the preceding study [17] ingesting fatty fish 3 times per week over 4 months were on a high risk of CHD (combined hyperlipidemia, mild hypertension most of them with metabolic syndrome).

The data of our present study correspond to the findings of other authors [15] who found a decrease of VPC by 48% after supplementing the diet with cod liver oil over 4 months and by 25% in a control group supplemented with sunflowerseed oil as placebo. An other group [14] likewise reported a diminution of VPC of more than 50% after 4 months of fish-oil supplementation the data being, however, insignificant because of the low number of subjects ($n = 9$).

Experimental data referring to the antiarrhythmic action of n-3 PUFA were thoroughly reviewed by Nair et al. [11] and Kang and Leaf [13]. It was postulated that n-3 PUFA simultaneously modify different factors. Consequently, it is impossible to attribute their beneficial effects to one single action [11]. Obviously, the accumulation of dietary n-3 PUFA in membrane phospholipids of cardiomyocytes are the supply from which these fatty acids are readily available as free acids to prevent arrhythmias following myocardial ischemia. In short, direct effects of FFA on myocardium, modified fatty acid composition of membrane phospholipids, alteration of the eicosanoid system, effects on the inositol lipid cycle, cell signalling, calcium channels, enzymes and receptors are involved in the antiarrhythmic action of n-3 PUFA [11,13].

It has been speculated that diminished ventricular arrhythmias might help to explain the reduced incidence of reinfarction and sudden cardiac death reported recently [5–9,35], the long-term dietary intake of nearly 1 g/day of n-3 PUFA being a reasonable regimen at low cost and little risk in clinical practice and under everyday conditions. This disagrees with the Cardiac Arrhythmias Suppression Trial (CAST) [36] that showed an even higher rate of death from arrhythmia in patients after myocardial infarction treated with antiarrhythmic drugs compared to patients assigned to placebo. Therefore, further clinical studies are necessary to elucidate the possible role of n-3 PUFA for reduced cardiac arrhythmias and a link with sudden cardiac death to define indications for their prevention under clinical conditions.

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