Effects of n–3 fatty acids from fish on premature ventricular complexes and heart rate in humans[1–3]

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ABSTRACT

Background: A large body of evidence suggests that n−3 fatty acids from fish prevent fatal heart disease. They may be an effective and safe alternative to drug treatment for reducing the risk of arrhythmia and sudden cardiac death.

Objective: We investigated the effect of n−3 fatty acids on heart rate and premature ventricular complexes (PVCs), a common form of arrhythmia that may trigger arrhythmias that are more life-threatening.

Design: Patients ($n = 84$) with ≥1440 PVCs/24 h in a previous Holter recording were randomly assigned to receive 1.5 g/d of either n−3 fatty acids or placebo. Two 24-h Holter recordings were made at baseline, and 2 were made after an intervention of ≈14 wk.

Results: Treatment did not significantly affect the number of PVCs. The number decreased in the fish-oil group by 867/24 h more than it decreased in placebo group (95% CI: −3187, 1453). However, the mean 24-h heart rate was significantly affected, decreasing in the fish-oil group by a mean of 2.1 beats/min more than it decreased in the placebo group (95% CI: −3.9, −0.3).

Conclusions: Supplementation with 1.5 g n−3 fatty acids/d from fish does not substantially suppress the number of PVCs in a patient population with frequent PVCs. However, n−3 fatty acids decreased heart rate by 2.1 beats/min, a significant decrease that predicts a lower risk of sudden death. *Am J Clin Nutr* 2005;81:416–20.

KEY WORDS Ambulatory electrocardiography, arrhythmia, fish oils, heart rate, n–3 fatty acids, sudden cardiac death, ventricular premature complexes

INTRODUCTION

Clinical trials show a beneficial effect of moderate intakes (≈1 g/d) of n−3 fatty acids on mortality and sudden cardiac death. This effect is seen within a few months after the beginning of treatment, but there is little or no effect on nonfatal events (1, 2). In addition, observational studies show strong inverse relations of fish consumption or blood concentrations of n−3 fatty acids with the incidence of fatal coronary artery disease and sudden cardiac death, but not with nonfatal heart disease (3–6). In addition, experimental studies have indicated that n−3 fatty acids increase the arrhythmia threshold and effectively prevent ventricular fibrillation in animal and in vitro models (7). Thus, results from different types of studies suggest that n−3 fatty acids have an immediate effect on arrhythmia rather than a slow effect via regression of atherosclerosis.

Frequent premature ventricular complexes (PVCs) are independent predictors of sudden cardiac death and mortality in patients with a history of myocardial infarction (MI), significant left ventricular (LV) dysfunction, or both (8–10). Moreover, in middle-aged men without prior symptoms of cardiovascular disease, frequent PVCs during exercise predicted long-term risk of cardiovascular death (11). However, there are no data that ambient PVCs are predictive of an adverse prognosis in patients without structural heart disease. n–3 Fatty acids might intervene in the occurrence of PVCs by slowing down the spontaneous beating rate or by prolonging the refractory period (7). PVCs are a common form of arrhythmia that are themselves innocent but that may trigger more serious arrhythmic events, such as ventricular tachycardia or ventricular fibrillation (12). Thus a reduction in PVCs results in fewer triggers and may in that way decrease the risk of more serious arrhythmic events. It should be noted, however, that effects on PVCs do not necessarily parallel effects on endpoints. In the Cardiac Arrhythmia Suppression Trial (CAST; 13), encainide and flecainide did reduce the number of PVCs but increased rather than decreased mortality. In contrast, it is conceivable that n−3 fatty acids prevent PVCs and at the same time reduce fatal arrhythmias and mortality. Therefore, if effective, n−3 fatty acids may be a safe alternative to drug treatment of arrhythmias.

A study by Sellmayer et al (14) suggested that n−3 fatty acids can reduce the incidence of PVC in patients with spontaneous PVCs. The mean ± SD number of PVCs decreased from 6937 ± 5192 at the beginning of the intervention to 3591 ± 3884 after 16 wk of intervention in the fish-oil group, whereas, in the placebo group, the number decreased from 6306 ± 3363 to 4728 ± 3320. Although the effects were impressive, this potentially important finding urgently required confirmation. In addition, n−3 fatty acids may reduce heart rate and in this way reduce the risk of

sudden death (15–17). Therefore, the aim of the current study was to investigate the effect of n−3 fatty acids on the incidence of PVCs and on heart rate in patients with frequent PVCs. Demonstration of an effect on PVCs would provide clues as to possible underlying mechanisms and may also add to the evidence that n−3 fatty acids prevent fatal heart disease by preventing serious ventricular arrhythmia.

SUBJECTS AND METHODS

Subjects

We defined frequent PVCs as an average of ≥1/min, or 1440/24 h. On that basis, cardiologists recruited and enrolled patients aged ≥18 y who had ≥1440 PVCs/24 h in a Holter recording made <6 mo before. Patients who used antiarrhythmic drugs other than β-blockers were excluded, as were those with known left ventricular dysfunction, sustained tachycardia, symptomatic ischemia, hemodynamically relevant valvular defects, or other cardiac diseases related to arrhythmia. Patients who had used any supplemental n−3 fatty acids during the previous 3 mo were also excluded.

Ninety-two patients who met the inclusion criteria were randomly assigned to receive n–3 fatty acids or placebo; 84 of the 92 successfully completed the study. One patient was excluded because of the use of prescribed antiarrhythmic medication, and one patient died during the study. Four patients dropped out for personal reasons, one because of perceived side effects, and one because of admission to the hospital.

The study protocol was approved by the Medical Ethics Committee of Wageningen University. Patients gave their written informed consent after the study protocol had been explained to them.

Design and treatment

This placebo-controlled, double-blind study with parallel design was conducted in 3 hospitals in the Netherlands. Patients were randomly assigned in blocks of 2 units, stratified for history of MI. Patients received a daily 3.5-g dose of either fish oil or placebo oil (high–oleic acid sunflower oil; Loders Croklaan, Wormerveer, Netherlands) during the intervention period of 14 ± 1 wk. The oils were administered daily in 7 soft gelatin capsules each containing 500 mg oil and 1.5 mg tocopherol as an antioxidant (Banner Pharmacaps Europe BV, Tilburg, Netherlands). The daily dose of fish oil provided ≈700 mg eicosapentaenoic acid (EPA; 20:5n–3), 560 mg docosahexaenoic acid (DHA; 22:6n–3), and 260 mg of other n−3 fatty acids. The placebo capsules contained mainly oleic acid (18:1n–9).

Data collection

Twenty-four-hour Holter recordings were made with SEER MC digital recorders (GE Medical Systems Information Technologies, Milwaukee). We averaged the results of 2 Holter recordings made at baseline and those of 2 Holter recordings made at the end of the study (in both cases, the 2 recordings were made 1 wk apart) to reduce the large variation in the occurrence of PVCs.

Data on demographics, medical history, and cardiac medication were collected at baseline and recorded on the case report form. Intakes of energy, fatty acids, cholesterol, and alcohol were estimated once during the intervention by a telephone-administered 24-h dietary recall. In addition, to assess and monitor their fish intake, patients were interviewed at baseline and at the end of the intervention with the use of a questionnaire on the frequency of fish consumption. Body mass index and blood pressure were monitored during the study. Patients recorded the intake of capsules in a diary. We took nonfasting blood samples a few days before the beginning of the treatment and during the last week of the intervention. Serum cholesteryl fatty acids were analyzed as described previously (18).

Holter analysis

The 24-h Holter recordings were analyzed with a Marquette Series 8000 Holter analyzer (GE Medical Systems Information Technologies) by an experienced Holter technician who was unaware of the treatments. Initially, all beats were automatically categorized into different classes on the basis of their morphology. The technician ensured that the classes were correctly identified. In addition, for each class containing >10 PVCs, all beats within that class were laid on top of each other (by layering the different electrocardiograms digitally on the screen) to check for possible misclassification of non-PVCs, and all outliers were removed. The frequency of PVCs was calculated by dividing the number of PVCs by the total time that the signal was of sufficiently high quality for analysis. The mean heart rate was calculated as the total number of normal beats in sinus rhythm (3 consecutive normal beats) divided by the recording duration after correction for noise and episodes of nonsinus rhythm.

Statistical analysis

A pretrial power calculation showed that 40 subjects per group would be sufficient to detect a significant difference ($P < 0.05$) in the change in numbers of PVCs in response to the intervention between the fish-oil and placebo groups with a power of 80%, if the real population effect exceeded 25%. The primary outcome of the study was the change in number of PVCs during the treatment. Differences in the changes in numbers of PVCs and heart rate between the fish-oil and placebo groups were analyzed by using Student's *t* test. Analysis of a subgroup of patients with and without prior MI was planned a priori and included in the protocol. Significance was set at $P < 0.05$. Statistical analyses were performed by using SPSS for WINDOWS software (version 10.0.5; SPSS, Chicago).

RESULTS

Differences in baseline characteristics between the fish-oil and the placebo groups were not significant (**Table 1**). Compliance was reflected by a mean change in the amount of EPA (in g/100 g total fatty acids) in serum cholesteryl esters during intervention of 181% in the fish-oil group and −2% in the placebo group. For DHA, the change was 49% in the fish-oil group and −5% in the placebo group (**Table 2**). Two patients in the fish-oil group and 2 in the placebo group stopped taking the capsules before the study was finished because they experienced side effects that they believed were due to the treatment: skin rashes, gastrointestinal complaints, and nausea (1 patient in each group). Analyses were performed including the data from these 4 patients, but results did not change when they were excluded.

The effect of treatment on the number of PVCs/24 h did not differ significantly between the fish-oil and placebo groups. The

TABLE 1
Characteristics at baseline of patients who completed the study[1]

	Placebo group (n = 43)	Fish-oil group (n = 41)
Age (y)	61 ± 13[2]	67 ± 13
Men [n (%)]	22 (51.2)	28 (68.3)
BMI (kg/m^2)	26 ± 4	26 ± 4
PVCs at screening (no./24 h)	7623 ± 7779	9553 ± 8896
Heart rate at screening (beats/min)	76 ± 11	71 ± 11
Dietary intake of n–3 fatty acids (ALA + EPA + DHA) from fish (g/mo)[3]	6.8 ± 7.7	9.3 ± 10.1
History of myocardial infarction [n (%)]	11 (25.6)	11 (26.8)
Use of β-adrenergic blocking agent [n (%)]	15 (34.9)	23 (56.1)

[1] PVCs, premature ventricular complexes; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid. There were no significant differences between groups (t test).

[2] $\bar{x}$ ± SD (all such values).

[3] ALA accounts for ≈20% of the n–3 fatty acid intake from fish.

number decreased by a mean of 867 (6%) more in the fish-oil group than in the placebo group (95% CI: −3187, 1453), as shown in **Table 3**. In the small subgroup of 22 patients with prior MI, the mean response was an increase of 2717 (+23%) more in the fish-oil group than in the placebo group (95% CI: −2254, 7689) (Table 3). In the subgroup of 62 patients without prior MI, the mean response was a decrease of 2129 (−22%) more in the fish-oil group than in the placebo group (95% CI: −4764, 507) (Table 3).

Twenty-four-hour mean heart rate decreased by an average of 2.1 beats/min more in the fish-oil group than in the placebo group, and this difference was significant (95% CI: −3.9, −0.3) (Table 3). Heart rate results in the subgroups with and without prior MI were very similar to those in the entire cohort (Table 3). Blood pressure and body mass index were not affected by treatment (data not shown).

Background dietary intake did not differ significantly between the 2 treatment groups. The fish-oil group consumed 33% of energy as fat, 0.6% of energy (1.4 g/d) as total n−3 fatty acids (mostly ALA), 4% of energy as alcohol, and 24 mg cholesterol/MJ. In the placebo group, the corresponding values were 33%, 0.5% (1.1 g/d), 5%, and 28 mg cholesterol/MJ. Fish intake did not

TABLE 2
The content of EPA and DHA as a percentage of total fatty acids in serum cholesteryl esters at the beginning and the end of the intervention and the response[1]

Treatment group[2]	Beginning of intervention	End of intervention	Response
EPA			
Fish-oil (n = 41)	1.28 ± 0.76	3.60 ± 1.65	2.32 ± 1.30
Placebo (n = 42)[3]	1.07 ± 0.69	1.06 ± 0.75	−0.02 ± 0.74
DHA			
Fish-oil (n = 41)	0.70 ± 0.20	1.04 ± 0.24	0.34 ± 0.19
Placebo (n = 42)[3]	0.64 ± 0.21	0.62 ± 0.19	−0.03 ± 0.13

[1] All values are $\bar{x}$ ± SD. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid. The EPA and DHA results in the fish-oil and placebo groups were significantly different, $P \leq 0.0001$ (t test).

[2] The fish-oil group received 3.5 g fish oil (1.5 g n−3 fatty acids); the placebo group received 3.5 g high–oleic acid sunflower oil.

[3] Serum fatty acid results are missing for 1 subject in the placebo group.

differ significantly between the treatment groups and did not change significantly during the intervention.

DISCUSSION

Daily intake of 1.5 g n−3 fatty acids for ≈14 wk did not significantly affect the number of PVCs in patients who had been experiencing frequent PVCs. In a clinical setting, an individual positive response to treatment can be defined as a reduction by >70% in the number of PVCs in a particular patient. In the current study, only 3 patients in the fish-oil group and 7 patients in the placebo group showed such a reduction. These results indicate that n−3 fatty acids from fish are not very effective in the treatment of PVCs in this study.

Sellmayer et al (14) tested the effects of the intake of 2.4 g n−3 fatty acids/d in 68 patients with a minimum of 2000 spontaneous PVCs/24 h. They found a reduction of > 70% in the number of PVCs in 15 patients (44%) after fish-oil intake and in 5 patients (15%) after placebo intake. Recently, a reduction in PVCs was seen after the intake for 6 mo of 1 g n−3 fatty acids/d in 33 patients with low numbers of PVCs (214 ± 76/24 h at baseline) (19). In contrast, a significant effect of n−3 fatty acids on the number of PVCs was absent in 3 other small studies (20–22). Even if we combine the results of all studies, it is still questionable whether n−3 fatty acids can indeed reduce PVCs.

Protective effects of n−3 fatty acids on hard endpoints in clinical trials have been found only for post-MI patients (2, 23, 24). In contrast, no effects or even adverse effects were found in a trial in 3114 angina patients who were advised to eat 2 portions of fatty fish each week or to ingest 3 g fish oil/d (25). It is hard to explain these adverse results, but it may be suggested that the cardioprotective effect of n−3 fatty acids is restricted to patients with earlier MI. n–3 Fatty acids may interact with structural abnormalities in hearts that have undergone MI and thus prevent fatal electrical events. Our population, overall, was low-risk: we excluded patients with LV dysfunction from the study, and only 25% of the subjects had a history of MI. When we restricted our analysis to this subgroup of 11 subjects per treatment, we saw a nonsignificant increase in PVCs in patients given n−3 fatty acids. Although power was limited for subgroup analyses, we have no indications that the mechanism behind the possible antiarrhythmic effect of n−3 fatty acids in these patients involves PVCs as potential arrhythmic triggers. However, the effects could be different in a higher-risk population, eg, patients with LV dysfunction.

n–3 Fatty acids significantly ($P = 0.022$) decreased heart rate by 2.1 beats/min. An observational study reported an inverse association between n−3 fatty acids and heart rate (26). Moreover, some intervention studies reported that n−3 fatty acids or DHA alone decrease heart rate in different patient populations by 2.2 to 3.5 beats/min (15–17). Increased heart rate is an independent risk factor for sudden death but not for fatal MI in middle-aged men free of known cardiovascular disease (27–30). On the basis of the work of Jouven et al (27), a decrease of 2.1 beats/min in heart rate would predict a risk reduction for sudden cardiac death of 6%. It can be speculated that n−3 fatty acids affect heart rate through stabilizing electrical activity of isolated cardiac myocytes by elevating the action potential threshold and prolonging relative refractory time (7). These actions may affect electrical stimulation of the sinus node resulting in a lower heart rate. However, n−3 fatty acids also may affect sympathetic and

TABLE 3
Number of premature ventricular complexes (PVCs) per 24 h and heart rate at the beginning and the end of the intervention period, the response to the intervention, and the difference in response between the fish-oil and placebo groups for all patients and for patients with and without prior myocardial infarction (MI)

Treatment group[1]	Beginning of intervention	End of intervention	Response	Difference
All patients				
PVCs				-867 $(-3187, 1453)$[3]
Fish-oil ($n = 41$)	$10\,803 \pm 9561$[2]	9425 ± 8183	-1378 ± 5368	
Placebo ($n = 43$)	7095 ± 8201	6585 ± 8267	-511 ± 5319	
Heart rate (beats/min)				-2.1 $(-3.9, -0.3)$
Fish-oil ($n = 41$)	69.8 ± 8.0	67.5 ± 7.8	-2.3 ± 3.6	
Placebo ($n = 43$)	73.9 ± 10.6	73.7 ± 9.9	-0.2 ± 4.5	
Patients with MI				
PVCs				2717 $(-2254, 7689)$
Fish-oil ($n = 11$)	$10\,388 \pm 10\,146$	$10\,281 \pm 9268$	-107 ± 5744	
Placebo ($n = 11$)	$11\,787 \pm 10\,697$	$8962 \pm 10\,528$	-2824 ± 5430	
Heart rate (beats/min)				-2.1 $(-5.2, 1.1)$
Fish-oil ($n = 11$)	64.3 ± 7.2	62.7 ± 7.0	-1.6 ± 2.9	
Placebo ($n = 11$)	71.6 ± 12.6	72.0 ± 12.5	0.5 ± 4.1	
Patients without MI				
PVCs				-2129 $(-4764, 507)$
Fish-oil ($n = 30$)	$10\,956 \pm 9513$	9112 ± 7898	-1844 ± 5247	
Placebo ($n = 32$)	5483 ± 6612	5767 ± 7359	284 ± 5126	
Heart rate (beats/min)				-2.1 $(-4.3, 0.5)$
Fish-oil ($n = 30$)	71.8 ± 7.4	69.2 ± 7.4	-2.6 ± 3.9	
Placebo ($n = 32$)	74.7 ± 10.0	74.2 ± 9.0	-0.5 ± 4.7	

[1] The fish-oil group received 3.5 g fish oil (1.5 g n–3 fatty acids); the placebo group received 3.5 g high–oleic acid sunflower oil.

[2] $\bar{x} \pm$ SD (all such values).

[3] $\bar{x}$; 95% CIs in parentheses.

parasympathetic control of heart rate by virtue of their interaction with the adrenergic system (31).

Baseline characteristics of the fish-oil and placebo groups were somewhat similar but not identical. The most important difference (although not a significant difference) is that the number of PVCs at screening was somewhat higher in the fish-oil group than in the placebo group. However, this difference would be expected to result in a larger, rather than smaller, decrease in the number of PVCs, because of regression to the mean or because higher numbers give more room for a decrease. In addition, we did find an effect of n−3 fatty acids on heart rate, despite differences in baseline characteristics between groups. Altogether, it seems unlikely that the lack of a distinct effect on the number of PVCs can be explained by baseline differences between the fish-oil and placebo groups.

The evidence from different types of studies suggesting that n−3 fatty acids may reduce serious ventricular arrhythmia risk justifies further research on this potentially protective mode of action (7). It is hoped that definitive answers will come from current long-term trials of n−3 fatty acids and arrhythmia incidence in high-risk patients with an implantable cardioverter defibrillator (ICD) (32). We are aware of 3 such trials, of which 1 recently reported preliminary results. This study in 200 subjects with an ICD showed a trend, over a 2-y follow-up, toward increased rather than decreased recurrence of ventricular arrhythmias in patients who received n−3 fatty acids during the study (33). The results of the other 2 ICD trials are required, before definitive conclusions can be drawn. In addition, in a pilot study, the immediate effect of n−3 fatty acids was assessed in patients with an ICD (34). Sustained ventricular tachycardia was not induced in 5 of 7 patients. This antiarrhythmic effect should be confirmed in a larger, randomized, placebo-controlled trial.

In the current randomized, double-blind study, dietary n−3 fatty acids significantly decreased heart rate by 2.1 beat/min, which predicts a lower risk of sudden death (27). However, n−3 fatty acids are apparently not very effective in the treatment of PVCs. This makes it less likely that the presumed effect of n−3 fatty acids on the risk of sudden cardiac death is mediated by a reduction in the frequency of triggers of arrhythmia. Nevertheless, further exploration of this hypothesis is warranted, and trials on life-threatening arrhythmia and mortality are needed to support dietary recommendations.

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