British Journal of Nutrition (2005), **93**, 787–790
DOI: 10.1079/BJN20051429

Short communication

Effect of *n*-3 fatty acids from fish on electrocardiographic characteristics in patients with frequent premature ventricular complexes

Anouk Geelen[1]*, Peter L. Zock[1], Ingeborg A. Brouwer[1], Martijn B. Katan[1], Jan A. Kors[2], Henk J. Ritsema van Eck[2] and Evert G. Schouten[1]

[1]*Wageningen Centre for Food Sciences (WCFS) and Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands*
[2]*Department of Medical Informatics, Faculty of Medicine and Health Sciences, Erasmus University Rotterdam, Rotterdam, The Netherlands*

(Received 1 September 2004 – Revised 23 December 2004 – Accepted 15 January 2005)

n-3 Fatty acids may protect against heart disease mortality by preventing fatal arrhythmias. Underlying effects on cardiac electrophysiology may be demonstrable in the standard electrocardiogram (ECG) and provide insight into the mechanism. Therefore, we investigated the effect of dietary *n*-3 fatty acids on heart-rate-corrected QT interval, T-loop width, spatial QRS-T angle and spatial U-wave amplitude in patients with frequent premature ventricular complexes. Seventy-four patients received either capsules providing 1·5 g *n*-3 fatty acids daily or placebo for approximately 14 weeks. ECG were recorded before and after intervention. None of the ECG characteristics was significantly affected by treatment. The present results do not provide additional support for the hypothesis that *n*-3 fatty acids prevent cardiac arrhythmia through generic electrophysiologic effects on heart cell membranes. However, we cannot exclude effects of *n*-3 fatty acids on clinical relevant endpoints that are not easily detected by prior changes in the ECG.

***n*-3 Fatty acids: Electrocardiogram: Heart-rate-corrected QT interval: Electrophysiology**

Evidence from human observational studies and clinical trials indicates that *n*-3 fatty acids can protect against fatal heart disease by preventing cardiac arrhythmias (Burr *et al.* 1989; Albert *et al.* 2002; Marchioli *et al.* 2002). In addition, experimental studies show that *n*-3 fatty acids prevent and terminate arrhythmias in *in vitro* and animal models. *n*-3 Fatty acids stabilize the electrical activity of cardiomyocytes by elevating the action potential threshold and prolonging the relative refractory time. These effects may result from an action of *n*-3 fatty acids on ion transport through heart cell membranes, which is essential for heart rhythm (Kang & Leaf, 2000). Effects on the electrophysiology of the whole heart may be demonstrable in a surface electrocardiogram (ECG) in man. We previously reported no effect of *n*-3 fatty acids on several ECG characteristics in healthy subjects (Geelen *et al.* 2002). However, effects of *n*-3 fatty acids may be detected only in abnormal ECG of more susceptible subjects. We therefore performed a study in patients with frequent premature ventricular complexes, a common form of arrhythmia that may trigger more life-threatening arrhythmias.

The heart-rate-corrected QT interval (QTc) on the ECG is a relevant measure for arrhythmia risk. In the general population, subjects with a longer QTc have an increased mortality risk (Schouten *et al.* 1991; Dekker *et al.* 1994; de-Bruyne *et al.* 1999). Thus, a decrease in QTc by *n*-3 fatty acids would support a protective effect of *n*-3 fatty acids on heart disease. An earlier study showed that *n*-3 fatty acids decreased the duration of QTc in dogs (Billman *et al.* 1997). *n*-3 Fatty acids may also affect other more exploratory ECG characteristics. For instance, T-loop width (Kors *et al.* 1999) and the spatial QRS-T angle (Kardys *et al.* 2003) have been proposed as markers for heterogeneity of ventricular repolarization, which provides the condition for the genesis of ventricular arrhythmias. The spatial QRS-T angle has been recognized as a risk predictor of cardiac mortality in the elderly (Kardys *et al.* 2003). Furthermore, U-wave changes may predict the occurrence of arrhythmias (Trusz-Gluza *et al.* 2002), although little is known about the origin and physiological meaning of the U-wave. In an earlier study on the effects of *n*-3 fatty acids on ECG characteristics (Geelen *et al.* 2002), we found a tendency for *n*-3 fatty acids to decrease the U-wave (S Quak, A Geelen, IA Brouwer, PL Zock, HJ Ritsema van Eck, JA Kors, MB Katan and EG Schouten, unpublished results). Effects of *n*-3 fatty acids on specific ECG characteristics could provide insight into the mechanism of a possible antiarrhythmic effect. It could also suggest new biomarkers for the study of the antiarrhythmic potential of drugs and food ingredients in man. Therefore, we investigated the effect of intake of very long-chain *n*-3 fatty acids from fish on QTc, T-loop width, spatial QRS-T angle and spatial U-wave amplitude in subjects with frequent premature ventricular complexes.

Subjects and methods

The Medical Ethical Committee of Wageningen University approved the study protocol. Patients gave their written informed

Abbreviations: ECG, electrocardiogram; QTc, heart-rate-corrected QT interval.

* **Corresponding author:** Dr Anouk Geelen, fax +31 317 483342, email anouk.geelen@wur.nl

consent after the study protocol had been explained to them. Cardiologists from three Dutch hospitals recruited and enrolled patients aged 18 years or older with at least 1440 premature ventricular complexes per 24 h in a previous Holter recording made less than 6 months before the study. We included patients with and without a history of myocardial infarction, but patients who used antiarrhythmic drugs other than beta-blockers were excluded. Ninety-two patients who met the inclusion criteria were randomized, of whom eighty-four successfully completed the study.

The primary purpose of the present double-blind, placebo-controlled study with parallel design was to investigate effects of *n*-3 fatty acids on the occurrence of premature ventricular complexes (results reported elsewhere). Patients were randomized per centre, stratified for history of myocardial infarction, to receive either a daily dose of 3·5 g fish oil or placebo oil (high oleic sunflower oil; Loders Croklaan, Wormerveer, The Netherlands) during the intervention period of 14 (SD 1) weeks. The oils were administered in seven soft gelatin capsules daily (Banner Pharmacaps Europe BV, Tilburg, The Netherlands). Fish oil capsules provided approximately 700 mg EPA (C20 : 5*n*-3), 560 mg DHA (C22 : 6*n*-3) and 260 mg other *n*-3 fatty acids per d. The placebo capsules contained mainly oleic acid (C18 : 1*n*-9).

Compliance of the patients was checked by analysis of *n*-3 fatty acids in serum cholesteryl esters from non-fasting blood samples taken at the beginning and end of the intervention period (Zock *et al.* 1997). Intakes of energy, fatty acids, cholesterol and alcohol were estimated by a telephone-administered 24 h dietary recall. In addition, fish intake was assessed twice by interviewing patients using a questionnaire on the frequency of fish consumption.

Complete ECG measurements at both baseline and the end of the intervention period were available for seventy-four patients. Standard twelve-lead ECG were recorded for 1 min with a Cardio Perfect Portable recorder and digitally stored on a Cardio Control workstation (Cardio Control NV, Delft, The Netherlands). We processed ECG recordings without knowledge of treatment type or other subject variables, using the Modular ECG Analysis System (MEANS; van-Bemmel *et al.* 1990). Bazett's formula ($QTc = QT/\sqrt{RR}$) was used to correct QT duration for heart rate. T-loop width and QRS-T angle were determined as described previously (Kors *et al.* 1999; Kardys *et al.* 2003). The amplitude of the spatial U-wave gradient vector was calculated by taking the integral of the x, y and z component of the U-wave using the interactive computer program 'Intraval' (Ritsema van Eck, 2004).

Differences in response between the fish oil and placebo groups were analysed by Student's *t* test. A subgroup analysis for patients with and without prior myocardial infarction was planned beforehand and included in the protocol.

Results

There were no substantial differences in baseline characteristics between the fish oil and the placebo group (Table 1). EPA in serum cholesteryl esters (g/100 g total fatty acids) confirmed compliance; it changed during intervention from 1·30 (SD 0·78) to 3·66 (SD 1·68) in the fish oil group and remained constant in the placebo group (1·03 (SD 0·70) to 0·98 (SD 0·62)). QTc was not significantly affected by intake of *n*-3 fatty acids; it decreased by 0·3 ms (95 % CI 10·7, 10·1 ms) or 0·1 % in the fish oil group compared with placebo (Fig. 1, Table 2). Intake of *n*-3 fatty acids also did not significantly affect T-loop width, spatial QRS-T angle and spatial U-wave amplitude (Table 2). Subgroup analyses in patients with and without prior myocardial infarction also revealed no significant effects (Table 2).

Table 1. Characteristics of the forty-four men and thirty women for whom complete electrocardiographic measurements were available

(Values are means and standard deviations unless indicated otherwise)

	Fish oil (*n* 38)		Placebo (*n* 36)	
	Mean	SD	Mean	SD
Age (years)	68	11	62	14
Male sex, *n* (%)	27 (71·1)		17 (47·2)	
BMI (kg/m^2)	27	4	26	3
Background *n*-3 fatty acid intake from fish* (g/month)	9·6	10·3	6·1	7·7
History of myocardial infarction, *n* (%)	11 (28·9)		8 (22·2)	

* Sum of α-linoleic acid plus EPA plus DHA.

Background dietary intake was similar in the two treatment groups. The fish oil group consumed 33 % energy as fat, 0·6 % energy (1·5 g/d) as total *n*-3 fatty acids (mostly α-linolenic acid), 4 % energy as alcohol and 23 mg cholesterol/MJ. In the placebo group the corresponding figures were 33 %, 0·5 % (1·1 g), 4 % and 28 mg/MJ. Fish intake was similar in the treatment groups and did not change during the intervention.

Discussion

We observed no effect of a daily intake of 3·5 g fish oil for approximately 14 weeks *v.* placebo on QTc, QRS-T angle, T-loop width or spatial U-wave amplitude in these patients with frequent premature ventricular complexes. It is unlikely that this is caused by a lack of power, because the 95 % CI of the difference in response of QTc was narrow. A true effect of *n*-3 fatty acids on QTc of more than 2·5 % is not expected. In a previous study, we also observed no effect of *n*-3 fatty acids on several ECG characteristics in eighty-four healthy middle-aged men and women (Geelen *et al.* 2002). The effects of *n*-3 fatty acids on the electrophysiology of the human heart may be too small to cause appreciable ECG changes or there may be multiple effects at the cellular level that cancel each other out in the ECG. A standard ECG of short duration (1 min) may not be useful to demonstrate possible effects of *n*-3 fatty acids on the heart.

Protective effects of *n*-3 fatty acids on hard endpoints in clinical trials have been found exclusively for post-myocardial

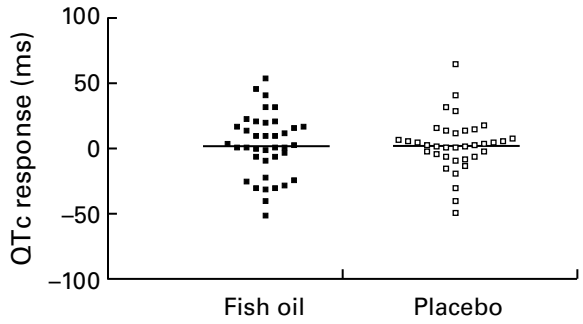

Fig. 1. Response of the heart-rate-corrected QT interval (QTc) of men and women who consumed 3·5 g fish oil/d (1·5 g *n*-3 fatty acids/d; *n* 38) or placebo (*n* 36) daily for approximately 14 weeks.

Table 2. Electrocardiographic characteristics at the start and end of the intervention period and the difference in response between the fish oil and placebo group, for all patients together and for the patients with and without prior myocardial infarction (MI) separately

(Values are means and standard deviations or mean and 95 % CI)

	Fish oil				Placebo				
	Baseline		End		Baseline		End		Difference in response
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean (95 % CI)
All patients	(*n* 38)				(*n* 36)				
QTc (ms)	437	22	438	28	435	22	437	26	−0·3 (−10·7, 10·1)
Spatial QRS-T angle (°)	78·9	44·2	76·2	49·4	70·9	37·6	67·9	39·3	0·4 (−8·0, 8·7)
Width of T-loop (°)	34·6	29·0	38·0	32·7	26·4	18·4	26·7	21·6	3·0 (−4·4, 10·5)
Spatial U-wave amplitude (μV)	25·3	34·8	19·1	11·4	24·3	30·6	19·5	29·8	−1·4 (−15·8, 13·0)
Patients with MI	(*n* 11)				(*n* 8)				
QTc (ms)	430	18	436	30	433	27	436	36	2·5 (−26·3, 31·3)
Spatial QRS-T angle (°)	91·3	42·5	88·9	56·3	114·3	27·0	116·0	27·5	−4·1 (−27·5, 19·2)
Width of T-loop (°)	51·2	39·6	50·6	38·7	40·6	20·9	41·3	23·6	−1·2 (−15·2, 12·9)
Spatial U-wave amplitude (μV)	32·8	60·4	22·8	15·7	38·5	50·5	24·2	30·7	4·4 (−40·3, 49·1)
Patients without MI	(*n* 27)				(*n* 28)				
QTc (ms)	439	24	440	27	436	21	437	24	−1·5 (−12·4, 9·4)
Spatial QRS-T angle (°)	73·9	44·7	71·1	46·4	58·5	30·5	54·1	30·4	1·6 (−7·0, 10·2)
Width of T-loop (°)	27·9	20·8	32·8	29·2	22·4	15·8	22·6	19·4	4·7 (−4·4, 13·7)
Spatial U-wave amplitude (μV)	22·2	16·8	17·5	9·0	20·2	21·7	18·1	29·9	−2·6 (−16·1, 10·9)

QTc, heart-rate-corrected QT duration.

infarction patients (Burr *et al.* 1989; GISSI-Prevenzione Investigators, 1999) and not in patients with angina (Burr *et al.* 2003). It could be hypothesized that the cardioprotective effect of *n*-3 fatty acids is restricted to patients with earlier myocardial infarction. *n*-3 Fatty acids may interact with structural abnormalities in cardiac tissue due to previous infarctions and in that way prevent fatal arrhythmias. If so, *n*-3 fatty acids would affect the ECG only in post-infarction patients. We did not find effects of *n*-3 fatty acids on the ECG in our subgroup of such patients; however, this group was small (*n* 19).

The dose of 3·5 g fish oil in the present study provided approximately 1·5 g *n*-3 fatty acids daily. Several observational studies suggest that the cardioprotective effect is already present at low doses of about 200 mg *n*-3 fatty acids/d. Most importantly, in the GISSI-Prevenzione trial, 1 g *n*-3 fatty acids/d was enough to lower the rate of death, non-fatal myocardial infarction and stroke (GISSI-Prevenzione Investigators, 1999). Thus, it is highly unlikely that the dose of *n*-3 fatty acids in the present study was too low to detect relevant effects on the ECG, if any exist.

A definitive answer as to whether *n*-3 fatty acids can reduce risk of ventricular arrhythmia will have to come from long-term trials on *n*-3 fatty acids and arrhythmia incidence in high-risk patients with an implantable cardioverter defibrillator (Brouwer *et al.* 2003). We are aware of three such trials; the first in 200 such patients recently reported a trend towards increased rather than decreased recurrence of ventricular arrhythmias in patients who received *n*-3 fatty acids over a follow-up of 2 years (Cleland *et al.* 2004). Two other trials are running and will report within 2 years.

Despite the body of evidence that *n*-3 fatty acids reduce risk of fatal heart disease by preventing ventricular arrhythmia, we could not demonstrate effects on cardiac electrophysiology as measured in body surface ECG. The present results do not provide additional support for the hypothesis that *n*-3 fatty acids prevent cardiac arrhythmia through generic electrophysiologic effects on heart cell membranes. However, we cannot exclude effects of *n*-3 fatty acids on clinical relevant endpoints that are not easily detected by prior changes in the ECG. Mechanistic studies at the organ level and clinical trials on endpoints will have to provide conclusive answers.

Acknowledgements

This work was funded by the Wageningen Centre for Food Sciences, an alliance of major Dutch food industries, Maastricht University, TNO Nutrition and Food Research, and Wageningen University and Research Centre, with financial support by the Dutch government.

References

Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC & Ma J (2002) Blood levels of long-chain *n*-3 fatty acids and the risk of sudden death. *N Engl J Med* **346**, 1113–1118.

Billman GE, Kang JX & Leaf A (1997) Prevention of ischemia-induced cardiac sudden death by *n*-3 polyunsaturated fatty acids in dogs. *Lipids* **32**, 1161–1168.

Brouwer IA, Zock PL, Wever EF, Hauer RN, Camm AJ, Bocker D, Otto-Terlouw P, Katan MB & Schouten EG (2003) Rationale and design of a randomised controlled clinical trial on supplemental intake of *n*-3 fatty acids and incidence of cardiac arrhythmia: SOFA. *Eur J Clin Nutr* **57**, 1323–1330.

Burr ML, Ashfield WP, Dunstan FDJ, Fehily AM, Breay P, Ashton T, Zotos PC, Haboubi NAA & Elwood PC (2003) Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* **57**, 193–200.

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC & Deadman NM (1989) Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* **2**, 757–761.

Cleland JG, Freemantle N, Kaye G, Nasir M, Velavan P, Lalukota K, Mudawi T, Shelton R, Clark AL & Coletta AP (2004) Clinical trials update from the American Heart Association meeting: Omega-3 fatty acids and arrhythmia risk in patients with an implantable defibrillator, ACTIV in CHF, VALIANT, the Hanover autologous bone marrow

transplantation study, SPORTIF V, ORBIT and PAD and DEFINITE. *Eur J Heart Fail* **6**, 109–115.

de-Bruyne MC, Hoes AW, Kors JA, Hofman A, van-Bemmel JH & Grobbee DE (1999) Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *Eur Heart J* **20**, 278–284.

Dekker JM, Schouten EG, Klootwijk P, Pool J & Kromhout D (1994) Association between QT interval and coronary heart disease in middle-aged and elderly men. The Zutphen Study. *Circulation* **90**, 779–785.

Geelen A, Brouwer IA, Zock PL, Kors JA, Swenne CA, Katan MB & Schouten EG (2002) (*N*-3) fatty acids do not affect electrocardiographic characteristics of healthy men and women. *J Nutr* **132**, 3051–3054.

GISSI-Prevenzione Investigators (1999) Dietary supplementation with *n*-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* **354**, 447–455.

Kang JX & Leaf A (2000) Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. *Am J Clin Nutr* **71**, 202S–207S.

Kardys I, Kors JA, van der Meer I, Hofman A, van der Kuip DA & Witteman JC (2003) Spatial QRS-T angle predicts cardiac death in a general population. *Eur Heart J* **24**, 1357–1364.

Kors JA, van-Herpen G & van-Bemmel JH (1999) QT dispersion as an attribute of T-loop morphology. *Circulation* **99**, 1458–1463.

Marchioli R, Barzi F, Bomba E, *et al.* (2002) Early protection against sudden death by *n*-3 polyunsaturated fatty acids after myocardial infarction – time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* **105**, 1897–1903.

Ritsema van Eck HJ (2004) Fiducial segment averaging to improve cardiac time interval estimates. *J Electrocardiol* **35**, Suppl., 89–93.

Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP & Pool J (1991) QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation* **84**, 1516–1523.

Trusz-Gluza M, Szydlo K, Kukla P, Wozniak-Skowerska I, Filipecki A, Peszek E & Wojcik E (2002) Postextrasystolic repolarization abnormalities in ST-U segment in patients with ventricular arrhythmias. *Ann Noninvasive Electrocardiol* **7**, 17–21.

van-Bemmel JH, Kors JA & van-Herpen G (1990) Methodology of the modular ECG analysis system MEANS. *Methods Inf Med* **29**, 346–353.

Zock PL, Mensink RP, Harryvan J, de-Vries JH & Katan MB (1997) Fatty acids in serum cholesteryl esters as quantitative biomarkers of dietary intake in humans. *Am J Epidemiol* **145**, 1114–1122.