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The effects of supplementation with omega-3 polyunsaturated fatty acids on cardiac rhythm: anti-arrhythmic, pro-arrhythmic, both or neither? It depends...

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Supplementation of omega-3 fatty acids (Ω-3) has been associated with a decreased cardiovascular risk, thereby concentrating attention on a potentially preventive effect regarding tachyarrhythmias and sudden cardiac death. However, recent randomized controlled trials challenge the efficacy of the additional application of Ω-3 and its anti-arrhythmic effect under certain clinical conditions. The present paper reflects the results of earlier and recent clinical studies with respect to the individual background conditions that may determine the clinical outcome of Ω-3 supplementation and thereby explain apparently conflicting clinical results. It is concluded that the efficacy of Ω-3 supplementation to prevent cardiac arrhythmias strongly depends on the underlying clinical and pharmacological conditions, a hypothesis that also is supported by data from experimental animal studies and by molecular interactions of Ω-3 at the cellular level.

Keywords: omega-3 unsaturated fatty acids, arrhythmia, prevention, cardiovascular disease, myocardial infarction, death, sudden

INTRODUCTION

It is a great desire of humans to find *golden ways* to solve major problems, especially to treat severe diseases effectively in order to prolong life, whenever possible without creating additional risks or side effects. In the past, omega-3 polyunsaturated fatty acids (Ω-3), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), appeared to be compounds having the potential to fulfill this dream, if supplemented to daily nutrition in sufficient amounts.

Consequently, a huge amount of data has been accumulated on this topic and many reviews and meta-analyses have been published (Bucher et al., 2002; Leaf et al., 2003; Whelton et al., 2004; Yzebe and Lievre, 2004; Dhein et al., 2005; Hooper et al., 2006; Reiffel and McDonald, 2006; Wang et al., 2006; Lombardi and Terranova, 2007; Cheng and Santoni, 2008; Jenkins et al., 2008a; León et al., 2008; Siddiqui et al., 2008; Marik and Varon, 2009; Zhao et al., 2009; Filion et al., 2010; Mozaffarian et al., 2011a).

Based on this background the purpose of the present paper is not to again review all the available data on Ω-3 effects or to discuss omega-3 unsaturated fatty acids as essential compounds in human and animal biology. This paper focuses on the effects of supplementation with Ω-3 on cardiac rhythm and discusses the potential clinical consequences of recent clinical studies that do not support the existence of this "golden Ω-3 way". Furthermore, the complexity of the biological interactions of Ω-3 as well as the variation of potential clinical settings are outlined in order to explain that supplementation with Ω-3 does not necessarily result in an overall beneficial clinical effect in every condition.

EARLIER CLINICAL STUDIES

An inverse relationship between consumption of fish oil and cardiovascular risk was shown in early observational, case–control, and cohort studies, with respect to the occurrence of cardiovascular disease (Whelton et al., 2004), sudden cardiac death (SCD) and non-SCD from coronary heart disease (Daviglus et al., 1997), and with regard to SCD in apparently healthy persons (Siscovick et al., 1995; Albert et al., 1998, 2002; Hu et al., 2002; Mozaffarian et al., 2003). Ω-3 levels in erythrocyte membranes were directly associated with a reduced rate of primary cardiac arrest (Siscovick et al., 1995). Similarly, elevated Ω-3 blood levels were associated with a reduced risk of sudden death among men without evidence of prior cardiovascular disease (Albert et al., 2002).

These data were supported by prospective and randomized nutritional intervention studies of secondary prevention after acute myocardial infarction (AMI). In the Diet and Reinfarction Trial (DART) a diet rich in fish and cereals was associated with a significant 29% reduction of all-cause mortality within 2 years after AMI (Burr et al., 1989). In the Lyon Diet Heart Study the Mediterranean diet group [diet enriched by alpha-linolenic acid (ALA, Ω-3) and olive oil, combined with an increased intake of

cereals, fresh fruit, vegetables and fish, but limited intake of saturated fatty acids and linoleic acid (Ω-6)] had a significantly lower rate of the combined endpoint cardiac death and non fatal myocardial infarction, if compared to the control group taking a prudent western-type diet ($p = 0.0001$; follow-up 27 months; de Lorgeril et al., 1994, 1998, 1999).

A predefined supplementation with Ω-3 was used in the large placebo-controlled, open labeled GISSI Prevenzione Trial (EPA + DHA 1 g/day, vitamin E 300 mg/day, a combination of both, or placebo; GISSI-Prevenzione Investigators, 1999), focusing on secondary prevention after AMI. In this study the intervention arms using Ω-3 showed a significant reduction of SCD – though this was not the primary endpoint of the GISSI Prevenzione Trial.

ANIMAL STUDIES

In parallel to these encouraging clinical data, animal studies (mostly using the rat or canine model) supported an anti-arrhythmic effect of Ω-3 especially with respect to ischemia-induced ventricular tachycardia (VT) or ventricular fibrillation (VF) (Matthan et al., 2005; Billman, 2006). The clearest effect in the prevention of VF by Ω-3 could be shown in infusion studies using a special experimental canine model. In this model acute myocardial ischemia was induced at a site distant from a previous myocardial infarction during submaximal exercise thereby activating the autonomic nervous system (Billman, 2006) and inducing VF.

However, these clear effects of Ω-3 under well-defined experimental conditions cannot simply be translated into the clinical situation, and several aspects have to be considered (Billman, 2006):

a. In this canine model not only superfusion with Ω-3 but also the application of β-receptor antagonists, calcium-channel blockers, and endurance exercise training – all interventions that are routinely used in actual clinical practice – were effective in VF prevention.
b. Not all dogs were susceptible to ischemia-induced VF in this model. Animals resistant to VF were characterized by reduced β-receptor responsiveness and an intact parasympathetic regulation, indicating that these are first line mechanisms to prevent ischemia-induced tachyarrhythmias.
c. Finally, incorporation of Ω-3 into the phospholipid bilayer can be expected to be significantly less in infusion studies as compared to feeding studies.

Feeding studies more closely may imitate the clinical situation, and under these conditions Ω-3 can be expected to exert their effect primarily after being incorporated into the cellular membrane. Numerous animal feeding studies have been published between 1987 and 1999, and the results showed a considerable heterogeneity. Still, a meta-analysis of these studies suggests fish oil does prevent ischemia and ischemia-reperfusion induced VT/VF (Matthan et al., 2005).

Heterogeneity of experimental results also can be seen in more recent studies. In isolated hearts of pigs fed with fish oil for 8 weeks, spontaneous ischemia-induced sustained VT/VF was facilitated in the Ω-3 group (Coronel et al., 2007). Other studies report increased resistance to ischemia-reperfusion injury after dietary Ω-3 application, which also could be a basis to protect against reperfusion arrhythmias (Abdukeyum et al., 2008; Zeghichi-Hamri et al., 2010).

RECENT CLINICAL STUDIES

The results of the animal studies and their apparent inconsistencies may be remembered when judging the data of recent prospective, randomized, double-blind clinical studies that interrupted the long list of positive results of older studies investigating the effect of Ω-3 on cardiovascular risk. In the following, these studies and the potential clinical consequences will be discussed in more detail.

1. Three randomized prospective studies evaluating the effect of high doses of Ω-3 in patients with ICD-devices failed to give homogeneous results.

   In one study recurrent VT events not due to myocardial ischemia were more common in patients treated with fish oil (1.3 g Ω-3 per day during a period of two years; $p < 0.007$; Raitt et al., 2005).

   However, in another study predominantly including patients with coronary artery disease, Ω-3 supplementation was associated with a significant risk reduction for the primary endpoint (time to first ICD-event or death from any cause) by 31% ($p = 0.033$). The death rates did not significantly differ between the study groups. Remarkably in this study no significant effect of Ω-3 could be shown in the subgroups of patients without coronary artery disease or with a left ventricular ejection fraction above 30% (Leaf et al., 2005a).

   Finally the SOFA-study did not show a significant effect of Ω-3 supplementation on the primary endpoint (appropriate ICD-interventions for recurrent VT/VF or death from any cause; hazard ratio 0.86, 95% CI 0.64–1.16). The majority of the patients included in the SOFA-study had coronary artery disease, more than 60% with previous myocardial infarction; almost 40% of the study participants had various forms of cardiomyopathy or valvular heart disease (Brouwer et al., 2006).

   In a meta-analysis of these three studies all-cause mortality did not significantly differ between the fish oil and the control groups (relative risk 0.70; 95% CI 0.42–1.15; Jenkins et al., 2008b).

   Finally, in a substudy of the GISSI-HF trial (566 heart failure patients with implanted ICD-devices, 57% with previous myocardial infarction, mean follow-up 928 days) a statistically non-significant trend toward a lower risk of ICD-discharge in patients treated with Ω-3 was shown [adjusted hazard ratio (HR) 0.80; 95% CI 0.59–1.09; $p = 0.152$]. However, mortality was similar in both groups [total mortality: Ω-3 (26.6%), placebo (24.3%); adjusted HR 1.25; 95% CI 0.89–1.75; $p = 0.19$; mortality for arrhythmias: Ω-3 (3.6%), placebo (2.1%); adjusted HR 1.84; 95% CI 0.67–5.05; Finzi et al., 2011]. Therefore the clinical significance of these data remains debatable.

   The apparent heterogeneity in the response of ICD-patients to fish oil supplementation could be a consequence of different study populations and different arrhythmic origins (ischemic versus non-ischemic). Heterogeneity also could be the result

of different concomitant medications of the study populations including β-blockers, digoxin, amiodarone, and sotalol. A potential influence of medication on the effect of fish oil supplementation may be indicated by the results of the DART 2 study (Burr et al., 2003).

2. In the controlled prospective DART 2 trial conducted with general practitioners of South Wales male patients with stable angina ($n = 3{,}114$, under 70 years of age) were randomly allocated to four study groups with specific nutritional advises including the advise to eat oily fish or take fish oil capsules in two of the study groups. Survival was measured during a follow-up of 3–9 years. The risk of SCD was significantly increased in the group taking oily fish or fish oil capsules (HR 1.54; 95% CI 1.06–2.23; Burr et al., 2003). The adverse effects of fish or fish oil capsules only occurred in men not taking beta-blockers or dihydropyridine calcium-channel blockers, and were increased in patients taking digoxin (Burr et al., 2005). Unfortunately, a conclusive interpretation of the DART 2 data is seriously limited as patient's recruitment and monitoring was interrupted for 1 year, long-term compliance was uncertain, and sudden death could not be ascertained in all cases (Burr et al., 2003).
3. In the large scale multicenter Japan EPA Lipid Intervention Study (JELIS; Yokoyama et al., 2007) consumption of 1.8 g EPA per day over a mean period of 4.6 years in hyperlipidemic patients (no AMI in the last 6 months, no serious heart disease) treated with statins resulted in a reduction of major cardiovascular events (combined endpoint including SCD, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina, angioplasty, stenting, or coronary bypass grafting) from 3.5 to 2.8% ($p = 0.011$; HR 0.81; 95% CI 0.69–0.95). However, there was neither a reduction of SCD (0.2% in both study arms; HR 1.06; 95% CI 0.55–20.07) nor of coronary death (0.3% in both study arms; HR 0.94; 95% CI 0.57–1.56) or all-cause death (control 2.8%, EPA-group 3.1%; HR 1.09; 95% CI 0.92–1.28). Compared to the GISSI Prevenzione Trial death rates and especially the rates of SCD were very low in both groups and therefore may be difficult to be reduced further by any intervention (rates for SCD: JELIS 0.2% in both groups; GISSI 2.2%/2.9% Ω-3 versus control; GISSI-Prevenzione Investigators, 1999). Furthermore, these low event rates may at least in part be the result of a high fish consumption of the Japanese population at baseline. As most risk reduction already occurs at about 250 mg EPA/DHA intake per day (Mozaffarian and Rimm, 2006), a further increase of Ω-3 intake may not have a substantial additional effect on cardiac death reduction (Mozaffarian, 2007).
4. In the Alpha-Omega-Study, a multicenter, double-blind, placebo-controlled trial, 4,837 patients in the chronic stable phase after myocardial infarction (average 3.7 years after AMI) and 60–80 years of age (21.8% women) were randomly assigned to one of four trial arms. Margarine was used in all trial arms, supplemented with either EPA/DHA (daily intake aimed to be 400 mg), alpha-linolenic acid (ALA, daily intake aimed to be 2 g), EPA/DHA + ALA, or placebo, respectively (Kromhout et al., 2010). After a follow-up of 40 months, 13.9% of the patients had a major cardiovascular event (death, non-fatal cardiovascular events, or cardiac intervention). The rates of the primary endpoint did not differ between the study groups. In addition, in all secondary endpoints, including ventricular-arrhythmia and total death, there was no significant difference between the study groups. Importantly, a high percentage of the patients received "state of the art medication," including statins.

   In a *post hoc* analysis after unblinding of the data in the subgroup of patients with diabetes ventricular-arrhythmia-related events tended to be reduced in the EPA/DHA group (HR 0.51; 95% CI 0.24–1.11) and significantly were reduced in the ALA group (HR 0.39; 95% CI 0.17–0.88). In a secondary analysis of the Alpha-Omega Trial taking high risk patients with previous myocardial infarction and diabetes the EPA/DHA + ALA group experienced significantly less ventricular-arrhythmia-related events (HR 0.16; 95% CI 0.04–0.69; Kromhout et al., 2011). These differential results support the necessity to exactly define the clinical conditions under which supplementation of Ω-3 may be beneficial.
5. In the OMEGA trial the effect of supplementation with 1 g/day of esterified EPA/DHA on the rate of SCD and other clinical events within 1 year after AMI was tested in 3,851 patients (25.6% female, mean age 64.0 years; Rauch et al., 2006, 2010). A 1-year follow-up was chosen, as the risk of cardiac death after AMI including a presumed arrhythmic death is highest in the first 3 months after the event (Solomon et al., 2005; Pouleur et al., 2010). Furthermore, in the GISSI trial, the significance in lowering SCD by Ω-3 had already been reached within 120 days (Marchioli et al., 2002). Following guidelines for the management of AMI and secondary prevention 77% of the patients in the OMEGA trial received acute percutaneous coronary intervention, and/or thrombolysis (8.3%). At hospital discharge the following medications were prescribed for almost all patients: beta-blockers (94%), ACE-inhibitors (83%), ARBs (8%), statins (94%), acetylsalicylic acid (95%), and clopidogrel (88%). Under these conditions, the rates of SCD were 1.5% in both study groups (OR 0.95; 95% CI 0.56–1.60) and total mortality was 4.6% in the Ω-3 group and 3.7% in the control group (OR 1.25; 95% CI 0.90–1.72). In none of the predefined secondary endpoints, including total death, major adverse cardiovascular and cerebrovascular events, and revascularization procedures in survivors, was found a significant difference between the study groups, and not even a trend in favor of the Ω-3 group could be observed. In addition, ICD-terminated VT or VF in survivors was 0.1% ($n = 2/1{,}654$) in the control group but 0.5% ($n = 9/1{,}705$) in the Ω-3 group [$p = 0.06$; OR (95% CI): 4.47 (0.97–20.74)]. Furthermore, there was no significant difference between the study groups with regard to SCD or total death in any of the predefined subgroups of patients with higher risk (diabetes, age >70 years, no acute revascularization, ejection fraction <35%).

   Despite these apparently homogeneous results their interpretation is limited as the case estimate in the OMEGA-study was based on an overestimation of the rate of SCD in the control group, thereby leading to an underpowering of the study.
6. Two other randomized controlled trials published recently also failed to show a clear beneficial effect of Ω-3 supplementation. In 563 elderly Norwegian men at high cardiovascular risk a non-significant tendency to a reduced all-cause mortality

could be observed (HR 0.53; 95% CI 0.27–1.04), but the rate of cardiovascular events remained unchanged (HR 0.89; 95% CI 0.55–1.45, follow-up 3 years; Einvik et al., 2010).

In 2,501 patients with a history of myocardial infarction, unstable angina or ischemic stroke supplementation with EPA/DHA was not associated with a significant decrease of major vascular events during a follow-up of 4.7 years (HR 1.08; 95% CI 0.79–1.47; Galan et al., 2010).

Which conclusions may be drawn from the clinical studies and the animal studies discussed above?

a. The effect of Ω-3 supplementation may depend on the background diet and the pre-existent intake of fish oil (Mozaffarian and Rimm, 2006; Reiffel and McDonald, 2006; Mozaffarian, 2007).
b. With regard to earlier studies, treatment of patients with coronary artery disease, especially treatment of patients with myocardial infarction has improved markedly. In the GISSI trial (inclusion period October 1993 to September 1995) only 4.4% of the patients had acute coronary revascularization at baseline, and only 4.7% were on cholesterol-lowering drugs at hospital discharge, increasing to only 46% after 42 months of follow-up (GISSI-Prevenzione Investigators, 1999). Furthermore, only 43.9% of the patients included in the GISSI trial were on beta-blocker treatment at the start of the study, and this percentage decreased during follow-up. It therefore may be speculated that up-to-date guideline adjusted treatment of AMI (including acute revascularization, medical treatment, and support of life style changes) may interfere with molecular and cellular Ω-3 interactions thereby weakening or competing with a potential beneficial Ω-3 effect. Although the available data not homogeneously support this hypothesis (Marchioli et al., 2007), this aspect should strongly be considered in future research.
c. The anti-arrhythmic effect of Ω-3 may depend on the pathophysiological conditions that facilitate arrhythmias. The clinical and experimental data outlined above suggest that Ω-3 supplementation may especially protect against ischemia-induced arrhythmias. Therefore, prevention of ischemia by modern treatments (i.e., revascularization, beta-blockers, statins, ACE-inhibitors, inhibition of thrombocyte aggregation, physical exercise) could attenuate a potentially beneficial effect of Ω-3. Beta-blockers are well known to prevent sudden death, and even statins could have some anti-arrhythmic effects (Anh and Marine, 2004; Lorenz et al., 2005).
d. Potential anti-arrhythmic effects of Ω-3 by augmentation of vagal activity (Mozaffarian et al., 2005; O'Keefe et al., 2006) may be blunted by beta-blocker treatment and increased physical training during cardiac rehabilitation (Nolan et al., 2008; Billman, 2009).

In summary, the anti-arrhythmic effect proven under experimental conditions in animal models and suggested in the earlier clinical studies appears to depend on the clinical conditions being studied. These clinical conditions are determined by the type and stage of the underlying myocardial disease and represent a sum of various pathophysiological conditions (including ischemia, reperfusion, ischemic preconditioning, scar tissue, inflammation, congenital defects, etc.) and the effects of modern medication including beta-blockers, ACE-inhibitors, statins, and other interventions potentially interfering with the arrhythmic risk, such as exercise training.

These considerations may also apply to the role of Ω-3 in the prevention of atrial fibrillation. Positive results (Mozaffarian et al., 2004, primary prevention in patients >65 years of age; Calò et al., 2005, patients undergoing coronary artery surgery; Macchia et al., 2008, postmyocardial infarction patients) were not confirmed in more recent studies and meta-analyses (Kowey et al., 2010; Saravanan et al., 2010; Bianconi et al., 2011; Farquharson et al., 2011; Liu et al., 2011). Still, it was demonstrated recently, that the use of fish oil (DHA 1.5 g and EPA 0.3 g daily) resulted in a prolongation and reduced dispersion of pulmonary venous and left atrial effective refractory periods in patients with paroxysmal atrial fibrillation (Kumar et al., 2011). Furthermore, in patients with persistent atrial fibrillation on amiodarone and a renin–angiotensin–aldosterone system inhibitor, taking Ω-3 (2 g/day) improved the probability of maintaining sinus rhythm after direct current cardioversion (Nodari et al., 2011). Similar to the prevention of ventricular tachyarrhythmias, prevention of atrial fibrillation therefore may depend on distinct clinical and pathophysiological conditions and concomitant medication. The ongoing OPERA-trial, including a total of 1,516 patients scheduled for cardiac surgery and in sinus rhythm, will give more insight into the potential role of Ω-3 supplementation to prevent post-operative atrial fibrillation (Mozaffarian et al., 2011b).

SOME ASPECTS OF THE MOLECULAR AND CELLULAR INTERACTIONS OF Ω-3 TO EXPLAIN HETEROGENEOUS CLINICAL RESULTS

For understanding the seemingly heterogeneous efficacy of Ω-3 supplementation in preventing tachyarrhythmias, it is important to reflect on their molecular and cellular interactions as has been delineated extensively in recent reviews (Leaf et al., 2003, 2005b; Dhein et al., 2005; McLennan and Abeywardena, 2005; Den Ruijter et al., 2007; Lombardi and Terranova, 2007; Siddiqui et al., 2008). In the following, only some aspects of potential relevance for interpretation of the clinical data are discussed:

There are three major ways in which Ω-3 may interfere with cellular and membrane function, thereby potentially moderating cardiac rhythm:

a. Direct interactions of Ω-3 with membrane bound proteins like the fast sodium channel, the voltage-gated L-type Ca^{2+} channel, specific potassium channels, and the Na^{+}/Ca^{++}-exchanger (Hallaq et al., 1990, 1992; Honore et al., 1994; Xiao et al., 1995, 1997; Kang and Leaf, 1996; Leifert et al., 1999; Leaf et al., 2003; Den Ruijter et al., 2007; Wang et al., 2010). Such interactions may occur predominantly with circulating Ω-3 when it is delivered by acute administration and infusion.
b. Incorporation into the phospholipid bilayer, thereby potentially changing membrane fluidity, and/or forming Ω-3 rich microdomains, and/or interacting with internal binding sites. This may result in a change of the function of membrane bound proteins like ion channels, receptors and signal transduction

systems (McMurchie et al., 1988; Croset and Kinsella, 1989; Kinoshita et al., 1994; Grynberg et al., 1996; Leifert et al., 1999, 2000b; McLennan, 2001; Den Ruijter et al., 2007). Incorporation into the cellular membranes predominantly is achieved by dietary long-term administration of Ω-3.

c. Interaction with intracellular pathways including gene expression and metabolism of phosphoinositides (Judé et al., 2006).

Circulating Ω-3 compounds are likely to have different electrophysiological effects, compared to Ω-3 incorporated into the membranes (Den Ruijter et al., 2007 for review). For example, peak cardiac sodium current was reduced by 51% after acute administration of EPA and DHA in neonatal rat cardiomyocytes (Xiao et al., 1995), but remained unaffected by Ω-3 incorporated in pig and rat cardiomyocytes (Leifert et al., 2000a; Verkerk et al., 2006). Differential effects of circulating versus incorporated Ω-3 have also been demonstrated with respect to various potassium channels and the regulation of calcium homeostasis (Den Ruijter et al., 2007 for review). Incorporated Ω-3, however, also may prevent further action potential (AP) shortening induced by circulating Ω-3. Patients with high levels of incorporated Ω-3 therefore may not have a further benefit from short term Ω-3 supplementation (Den Ruijter et al., 2010). This could be of a direct clinical relevance, as acute Ω-3 supplementation may be used for prevention of atrial fibrillation induced by cardiac surgery, which is being investigated in the OPERA-trial (Mozaffarian et al., 2011b).

Apart from these considerations the molecular interactions of Ω-3 and their effects on cardiac rhythm may be influenced by a large variety of additional conditions:

a. The various kinds of Ω-3 formulations being used (re-esterified triacylglycerides, ethyl-esters or phospholipids; Neubronner et al., 2011; Schuchardt et al., 2011).
b. The activity state of membrane bound proteins and ligand occupation of specific receptors involved in signal transduction (Rauch et al., 1989; Xiao et al., 1998; Den Ruijter et al., 2007), or the increased responsiveness of inhibitory G-proteins after ischemic preconditioning (Niroomand et al., 1995).
c. The activity of cellular phospholipases and the presence of lysophosphatides that change phospholipid environment and function of membrane bound proteins (Chien et al., 1981; Corr et al., 1984; Rauch et al., 1994), and may even vary between different myocardial regions depending on the degree of ischemia and/or inflammation.
d. The heterogeneity of electrical stability of myocardial cells in the diseased heart muscle due to regional differences with regard to various degrees of ischemia and tissue damage, ischemic preconditioning, etc. (Dhein et al., 2005). In this respect it should also be remembered, that in patients with coronary artery disease, myocardium is not presenting as a homogeneous and healthy tissue experiencing acute ischemia in a well-defined area, but rather as a mixture of healthy myocardium, hypertrophied tissue, scar tissue, and ischemic myocardium and includes areas of tissue with ischemic preconditioning, inflammation, various degrees of membrane phospholipid degradation and with more or less acute or chronic stretch, etc. (Janse et al., 2003).
e. The species (human, various animals) being studied. The characteristics of APs vary significantly between human and various animal myocardial cells and with gender (Karagueuzian et al., 1982; Shattock and Bers, 1989; Cheng, 2006; Tanaka et al., 2008).
f. The various mechanisms that trigger VT and VF. Under clinical conditions VT or VF are predominantly caused by triggered activity or by re-entry mechanisms. Fish oil shortens cardiac AP and accentuates the AP notch, which may lead to depression or even loss of the AP dome (Verkerk et al., 2006, 2007). Under clinical conditions where the AP is prolonged triggered activity may be the predominant pro-arrhythmic mechanism, which could be inhibited in isolated cardiomyocytes from rabbits and from patients with end stage heart failure by superfusion with Ω-3 (Den Ruijter et al., 2008). Triggered activity also could be inhibited in pig cardiomyocytes (Den Ruijter et al., 2006). In keeping with these experimental results Ω-3 were effective in reducing the arrhythmic risk in patients with idiopathic dilated cardiomyopathy (Nodari et al., 2009).
Conversely, AP shortening also may be pro-arrhythmic by reducing the refractory period and thereby promoting re-entry. Supplementation with Ω-3 may increase a preexisting heterogeneity in AP duration and repolarization (Verkerk et al., 2007), as can be seen, for example, in acute ischemia (Yan et al., 2004). In this way the occurrence of unidirectional block and re-entry may be facilitated (Janse and Wit, 1989). In the clinical situation therefore supplementation with Ω-3 may prevent or facilitate ventricular tachyarrhythmias depending on the predominant underlying arrhythmic mechanism (Den Ruijter et al., 2007).

Based on these considerations it becomes apparent that Ω-3 do not have a specific way to act, but rather possess multiple sites of potential actions, that may be influenced by a number of external conditions at the cellular and molecular level. Multiple sites of interaction between Ω-3 and myocardial tissue in combination with various possible ways of interference with these biochemical interactions are unlikely to result in an unequivocally predictable and homogeneous beneficial effect on clinical outcomes.

CONCLUDING REMARKS

Ω-3 clearly interfere with the physiology of myocardial cell membranes through a variety of specific and unspecific pathways, and thereby exhibit anti-arrhythmic effects under certain well-defined experimental and clinical conditions. However, these membrane effects of Ω-3 are complex. This complexity makes it difficult to predict the effects of Ω-3 supplementation on cardiac rhythm within the wide variety of conditions that represent clinical practice. For the future it will be necessary to define exactly the clinical conditions in which supplementation with of Ω-3 is beneficial, and without potentially harmful effects.

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