Special Report

Omega-3 Fatty Acids and Cardiac Arrhythmias: Prior Studies and Recommendations for Future Research

A Report from the National Heart, Lung, and Blood Institute and Office of Dietary Supplements Omega-3 Fatty Acids and Their Role in Cardiac Arrhythmogenesis Workshop

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Compared with prehistoric times, the ratio of n-6 to n-3 fatty acids in the modern diet has increased ≈10-fold to 20:1.[1,2] A substantial body of evidence suggests that n-3 polyunsaturated fatty acids (PUFAs) provide cardiovascular protection and prevent arrhythmias.[3–5] This has led to the recommendation by the American Heart Association that all adults eat fatty fish at least 2 times per week and that patients with coronary heart disease (CHD) are advised to consume ≈1 g/d of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) combined.[6,7] The evidence base is not entirely consistent, and a number of randomized trials have failed to show a protective effect of n-3 PUFAs against arrhythmias.[8–10] This has led to some uncertainty regarding the appropriate recommendations for their use.[11]

The present review originates from the Omega-3 Fatty Acids and Their Role in Cardiac Arrhythmogenesis Workshop sponsored by the National Heart, Lung, and Blood Institute and the Office of Dietary Supplements on August 29–30, 2005, and includes the findings from the recently published trials. Data from epidemiological studies, randomized clinical trials, animal studies, and basic science mechanistic studies on the role of n-3 PUFAs in arrhythmia prevention are examined. Areas in which the data are conflicting or our current knowledge is lacking are emphasized.

Fatty Acid Metabolism

Fatty acids are classified by the length of the carbon chain (long chain, n=20 to 22; intermediate chain, n=18) and the number of double bonds (saturated, monounsaturated, polyunsaturated).[1,2] For PUFAs, the location of the first double bond relative to the -CH_3 or omega (n-) end is given. Long- and intermediate-chain fatty acids must be ingested as part of the diet because they cannot be synthesized by humans and are therefore referred to as essential. The most common dietary fatty acids include (1) the omega-6 linoleic acid 18:2 (n-6) found in corn oil, safflower oil, peanuts, and soybeans; (2) the long-chain omega-3 fatty acids including EPA 20:5 (n-3) and DHA 22:6 (n-3) found predominantly in fish oils; and (3) the intermediate-chain fatty omega-3 fatty acid alpha-linolenic acid (ALA) 18:3 (n-3) found in flaxseed oil, canola oil, and walnuts. ALA can be converted into EPA by the enzyme delta-6 desaturase, although the efficacy appears to vary considerably among different individuals.[12] Competition between n-3 and n-6 dietary fatty acids influences the tissue proportions of n-3 and n-6 highly unsaturated fatty acids, which can be monitored and predicted in animals and humans (see http://efaeducation.nih.gov/sig/hufacalc.html).[13]

Fatty acids are an important source of energy in mammals and are the major energy source for the heart. In addition, fatty acids are converted into bioactive eicosanoids (eg, leukotrienes, prostaglandins, and thromboxanes) whose cardiovascular effects differ depending on the parent compounds.

Clinical Trials

Long-Chain n-3 Fatty Acids and Ventricular Arrhythmias

Observational Data

Coronary Heart Disease

A large body of observational data from epidemiological studies has accumulated over many years in support of the hypothesis that increased consumption of the long-chain n-3

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PUFAs found in fish, most notably EPA and DHA, lowers the risk of dying from CHD.[5,6] In the 1970s, Danish investigators first proposed that the low rate of CHD death observed among the Greenland Inuits was due to the abundance of n-3 fatty acids from seafood in their diet, which was estimated to be 400 g/d.[14] Similarly low CHD death rates were also found in the Japanese, particularly in Okinawa, where fish consumption is twice as high as in mainland Japan.[15] These cross-sectional ecological studies were followed by a large number of prospective epidemiological investigations regarding the association between fish intake and CHD. Most[16,17] but not all[18–21] prospective cohort studies reported inverse associations between fish consumption and CHD mortality. In general, high levels of fish intake have been associated with lower risks of CHD death in populations in which a substantial proportion of the population rarely or never consumed fish. In a recent meta-analysis combining these cohort studies, a 7% lower risk of CHD mortality was observed for each 20-g/d increase in fish intake (P for trend=0.03).[22] In contrast, the few studies that have examined nonfatal CHD end points have found either no[18,23,24] or weaker[25] associations with nonfatal myocardial infarction (MI), and when combined in meta-analysis,[22] the results for nonfatal MI are null. A recent study published after this meta-analysis, which was performed in a Japanese population, found a significant association between very high levels of dietary fish intake (≈8 fish meals per week) and nonfatal coronary events compared with those with lower levels (≈1 fish meal per week), suggesting that there may be antithrombotic or atherogenic actions at higher doses of fish intake.[26]

A potential antiarrhythmic action of low doses of n-3 fatty acids could explain, at least in part, this differential effect on fatal versus nonfatal CHD events at dosages of fish intake traditionally observed in Western populations. If n-3 fatty acids specifically reduce the risk of fatal ventricular arrhythmias associated with CHD, rather than the development of CHD, a preferential effect on CHD mortality would be expected.

Sudden Cardiac Death

If the n-3 fatty acids have antiarrhythmic properties, one would hypothesize that these fatty acids should have their greatest impact on risk of sudden cardiac death (SCD) because ventricular arrhythmias underlie ≈80% to ≈90% of these deaths.[27,28] Indeed, the 4 observational studies that have specifically examined the association between dietary intake of long-chain n-3 fatty acids and SCD have all reported protective associations. Siscovick et al[29] first reported an inverse association between dietary intake and blood levels of n-3 fatty acids and the risk of primary cardiac arrest utilizing a retrospective population-based case-control design. These data have subsequently been confirmed in 2 prospective cohort studies of male health professionals[23,30] and another study conducted among older individuals (aged >65 years).[24] In all of these studies, consuming fish ≈1 to 2 times per week was associated with significant 42% to 50% reductions in SCD risk.[23,24,29,30] In 2 of these studies, the benefits were even more striking when n-3 fatty acids were measured directly in blood.[29,31] Those in the highest quartile of n-3 fatty acid blood level were found to have 81% to 90% reductions in SCD risk compared with those in the lowest quartile, even after adjustment for other fatty acids. Of note, all of these studies were performed in populations who were apparently healthy and free of known CHD at inception.

Significant limitations are present in these observational studies. In most of them, SCD was assumed to be the result of MI and was included in the CHD end point. This is usually but not always the case. In addition, death certificates were often used to determine the cause of death. These limitations may account for some of the variability in study results.

Randomized Trials

Patients With Prior CHD

In addition to these observational studies, several randomized treatment trials utilizing long-chain n-3 fatty acids have been conducted among patients with known preexisting cardiac disease. Two of the largest randomized trials have involved dietary interventions. The first such trial, the Diet and Reinfarction Trial (DART) published in 1989, randomly assigned 2033 men after MI to receive or to not receive advice to eat at least 2 portions of fatty fish per week.[32] The men assigned to the fish advice arm experienced a 29% reduction in total mortality (primarily composed of CHD deaths) without any benefit on nonfatal MI. These results, in combination with the observational data described above, provided further support to the hypothesis that these agents might possess antiarrhythmic properties. In contrast, the follow-up DART-2 trial, which was conducted among 3114 men with self-reported "chronic angina," found a 26% higher risk of cardiac death and a 54% increased risk of SCD among men randomly assigned to the fish advice group.[33] However, this second trial had an interruption of the study for 1 year because of inadequate funds and a rerandomization. The effect that the study interruption had on dietary patterns and lost to follow-up rates is unknown, but it likely had some impact on the validity of these results.

Several trials have also tested the efficacy of n-3 fatty acid supplements, and the data on all these trials have been reviewed elsewhere recently.[34] By far, the largest published trial to date is the Gruppo Italiano per la Sperimentazione della Streptochinasi nell'Infarto miocardico (GISSI)-Prevenzione trial, which tested a combination of 850 mg EPA and DHA daily in an open-label fashion among 11 324 patients with recent MI.[35] The patients assigned to n-3 PUFA had a significant reduction in the primary end point (death, nonfatal MI, and nonfatal stroke), primarily because of a statistically significant reduction in SCD (45%) without any benefit on nonfatal MI or stroke. The survival curves for n-3 PUFA treatment diverged early after randomization. Total mortality was significantly lower after 3 months of treatment, and the reduction in risk of sudden death was already statistically significant at 4 months (relative risk, 0.47; P=0.048).[36] The authors concluded that this early effect of low-dose (1 g/d) n-3 PUFAs on total mortality and sudden death lends further support to the postulated antiarrhythmic mechanism of the n-3 fatty acids. Subsequent subgroup analyses from this trial suggested that the benefit on SCD risk may be greater among patients with systolic dysfunction (left

ventricular ejection fraction ≤40%) compared with those with preserved left ventricular ejection fraction (left ventricular ejection fraction >50%).[37] Although the GISSI-Prevenzione trial is the largest trial published to date, its open label design and lack of an appropriate placebo control group are important limitations.

On the basis of the data from observational epidemiological studies and the aforementioned randomized clinical trials, as well as plausible mechanisms for benefit, the American Heart Association in 2002 and 2003 recommended that all adults eat fish, particularly fatty fish, at least 2 times per week.[6,7] On the basis primarily on the results of the GISSI-Prevenzione trial, patients with CHD are advised to consume ≈1 g/d of EPA and DHA combined.[7]

Unpublished, Ongoing, or Planned Randomized Trials With Cardiovascular End Points

Preliminary results have recently become available from another large-scale randomized trial, the Japan EPA Lipid Intervention Study (JELIS), presented at the 2005 American Heart Association meetings in Dallas.[38] This trial enrolled 18 645 participants with hypercholesterolemia, of which 14 981 had no history of CHD, to high-dose EPA (1.8 g/d) in combination with statins versus a statin alone. At the time of presentation, the authors reported a 19% reduction in a composite CHD end point including SCD, MI, unstable angina, and coronary revascularization. Data on cause-specific event rates are not yet available. Of note, this trial will be one of the first large-scale primary prevention trials of the long-chain n-3 fatty acids.

In addition to this recently completed trial, several planned or ongoing large-scale randomized trials in Europe involve various cardiovascular end points as outcomes. Only 1 trial, the Omega trial, plans to examine SCD as the primary end point. This trial seeks to randomize 3800 patients with a recent MI to 1 g of long-chain n-3 fatty acids or placebo. Several other planned trials will examine composite end points, with SCD as a secondary end point. As a follow-up to the GISSI-Prevenzione trial, the GISSI-Heart Failure trial has already randomized, in a double-blind 2×2 factorial design, a heterogeneous group of ≈7000 patients with class II to IV heart failure (≈50% have a CHD etiology for congestive heart failure) to receive either 1 g of EPA/DHA, rosuvastatin, both active drugs, or both placebos.[39] The primary end point in this trial will be all-cause mortality or hospitalizations for cardiovascular reasons. Two other large-scale randomized trials are also planned in diabetic patients. The A Study of Cardiovascular Events in Diabetes (ASCEND) trial plans to randomize 10 000 diabetic patients in a 2×2 factorial design to low-dose aspirin versus 1 g long-chain omega-3 fatty acid supplementation versus placebo, and the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial plans to enroll 10 000 diabetic patients with a history of cardiovascular disease to insulin glargine versus 1 g long-chain omega-3 fatty acid supplementation versus placebo. Both trials will examine composite end points involving all serious cardiovascular events.

Trials in Patients With ICDs and a History of Ventricular Tachycardia/Ventricular Fibrillation: Primary Ventricular Arrhythmia End Points

The reduction in SCD risk reported in observational studies and clinical trials, along with the basic science data, has led many to hypothesize that these long-chain n-3 fatty acids are antiarrhythmic in humans and thus may prevent ventricular arrhythmias in high-risk patients. Although SCD is often the result of a ventricular arrhythmia, other processes are involved, and the trials outlined in the prior section have been unable to definitively decipher the mechanism(s) of action of these long-chain n-3 fatty acids. The growing use and capabilities of implantable cardioverter-defibrillators (ICDs) have created a unique research opportunity to begin to determine whether these long-chain n-3 fatty acids specifically reduce ventricular arrhythmias. On this basis, 3 separate groups of investigators undertook double-blind, randomized trials among ICD patients who had already experienced a life-threatening ventricular tachycardia/ventricular fibrillation (VT/VF) event.

The first trial, published by Raitt et al,[10] reported that fish oil did not reduce the risk of VT/VF in 200 ICD patients with an episode of VT/VF in the preceding 3 months enrolled in 6 US centers. At 12 months after randomization, 51% of patients assigned to 1.8 g of fish oil (1.3 g of combined EPA plus DHA) received ICD therapies for VT/VF compared with 41% of patients on placebo (olive oil; $P=0.19$). The trial also found an unexpected increased risk of recurrent VT/VF in the fish oil arm among a subgroup of 133 patients whose qualifying arrhythmia was VT (66% versus 43% experienced an episode of VT/VF at 12 months for fish oil versus placebo; $P<0.007$). Although the relative risk estimates for this group differed when compared with those who had VF as the index event, confidence intervals overlapped, and a formal test for interaction was not reported.

The second trial, the Fatty Acid Arrhythmia Trial (FAAT), reported contrary results in a group of 400 ICD patients enrolled at 18 US centers who had either a history of sustained VT/VF or syncope with sustained VT/VF at electrophysiological testing in the past 12 months.[9] The patients who were assigned to 4 g of fish oil per day (2.6 g of combined EPA plus DHA) had a trend toward a prolonged time to the first ICD event (VT or VF) or death from any cause (risk reduction, 28%; $P=0.057$) at 12 months compared with those assigned to placebo (olive oil). Twenty-eight percent of patients in the fish oil arm (n=57) and 39% of patients in the olive oil arm (n=78) had reached the primary end point when the trial was completed at 12 months. When therapies for "probable" episodes of VT or VF were included, the risk reduction became significant (31%; $P=0.033$). This trial was limited by a high noncompliance rate (35%). When patients who stayed on the protocol for at least 11 months were analyzed separately, the antiarrhythmic benefit of fish oil was greater (risk reduction, 38%; $P=0.034$). In subgroup analyses, the benefit appeared to be observed primarily among those with left ventricular ejection fractions ≤30% or those with a history of coronary artery disease, although the CIs overlapped, and tests for interaction were not significant.

The final trial, the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA), enrolled a group of 546 ICD patients in Europe who had an episode of sustained VT/VF within the last 12 months.[8] Patients were randomized to 2 g/d of fish oil (0.9 g EPA plus DHA) or placebo (sunflower oil) for a period of up to 12 months. After a median follow-up of 356 days, 30% of the patients in the fish oil group had experienced either VT/VF or death compared with 33% of the patients in the placebo group ($P=0.33$). Among the subgroup of 332 patients who previously had a MI, there was a tendency toward a beneficial effect of fish oil (hazard ratio, 0.76; 95% confidence interval, 0.52 to 1.11; $P=0.13$). In this subgroup, 28% of the patients on fish oil experienced either a life-threatening arrhythmia or death compared with 35% of the patients on placebo. Neither the FAAT nor SOFA trials found evidence for an increase in risk of VT/VF among patients whose qualifying event was VT.

The disparate results of these 3 ICD trials are not explained easily. The dosage of EPA/DHA in the FAAT trial was ≈2 times the dose in the other 2 trials; perhaps more importantly, patients were not allowed to eat >2 fish meals a month in the FAAT trial.[8–10] Patients in the Raitt and SOFA trials were allowed to eat 1 fish meal per week, an amount that has been associated with reductions in SCD risk in epidemiological studies. In the Physicians' Health Study, the magnitude of the risk reduction did not appear to differ substantially at levels of consumption >1 fish serving per week, suggesting a possible threshold effect.[23] Because patients were allowed to eat more fish, baseline n-3 fatty acid levels in red blood cells were significantly higher in the Raitt trial (4.7%) than in the FAAT trial (3.4%). When these levels are compared with those measured in the observational studies,[29,31] the FAAT trial levels would be comparable to those observed among participants in the lowest quartile of red blood cell n-3 fatty acids, and the Raitt trial would be comparable to those seen in participants in the second quartile of red blood cell n-3 fatty acids. In these observational studies, the participants in the second quartile had a significantly lower risk of SCD (48% to 50% reductions in risk) than those in the first quartile.[29,31] Thus, the participants enrolled in the Raitt trial may have been less likely to derive a benefit from fish oil supplementation than those enrolled in the FAAT study.

In addition, patients who have experienced a sustained episode of VT/VF requiring ICD placement are a somewhat heterogeneous group of patients; it is possible that although inclusion criteria in these studies were similar, the diversity of patients may not have been well balanced between the studies. Patients with ischemic cardiomyopathy predominated (≈60% to 70%), but patients with a variety of nonischemic cardiomyopathies (idiopathic, valvular, hypertrophic, and/or right ventricular) and smaller fractions of patients with structurally normal hearts who may or may not have had a known ion-channelopathy (eg, inherited long-QT or Brugada syndrome) were also included. Mechanisms underlying the initiation and propagation of ventricular arrhythmias differ in these different disease states, and fish oil may or may not be antiarrhythmic in each setting. Two of the trials (FAAT and SOFA) found that the benefit of fish oil may have been greater among post-MI patients or those with CHD,[8,9] whereas 2 trials also suggested that patients with low ejection fraction may benefit the most (FAAT and GISSI).[9,37] Unexpectedly, 2 of the aforementioned clinical trials (Raitt et al,[10] DART-2[33]) raised the possibility that fish oil may be proarrhythmic in some settings.

Most of the prior animal work has been performed in ischemia-mediated models, and clinical trials suggesting a benefit of fish oils on SCD risk were done in post-MI populations in which ischemia-induced ventricular arrhythmias would be expected to predominate. Even in the relatively healthy populations enrolled in the observational studies, coronary ischemia would be the most likely setting in which SCD occurs. Because patients with out-of-hospital sustained VT and/or VF usually undergo a thorough evaluation for coronary ischemia and adequate revascularization before implantation of an ICD, a significant number of subsequent arrhythmias in ICD patients may not be ischemically mediated. Even among those with CHD, scar-related reentry may be a common mechanism.

Finally, the marked difference in the event rates between the published patient populations further supports the possibility that patients enrolled in these trials differed in clinically meaningful ways. The Raitt trial, which had a much higher event rate, excluded patients on antiarrhythmic drug therapy and required patients to have an event within the last 3 months, whereas the FAAT and SOFA trials included patients on antiarrhythmic drugs and those with an event within the past 12 months. In addition, because none of the trials required specific device programming and each incorporated appropriate antitachycardia pacing therapies as well as shocks into the primary end point, some of the VT episodes may have been clinically insignificant arrhythmias that would have otherwise self-terminated and not resulted in SCD.[40] On the basis of variations in clinical practice between the centers, these types of arrhythmias may not have been well balanced between the trials.

Noninvasive Predictors of Arrhythmic Risk

Resting heart rate and heart rate profile during exercise have been associated with SCD risk.[41] In an observational study of 6565 men, subjects with a resting heart rate >75 bpm were at a 3.9-fold increased risk of SCD,[42] and a recent meta-analysis of 30 randomized trials demonstrated that fish oil decreased resting heart rate by 2.5 bpm ($P<0.001$) among those with baseline heart rates ≥69 bpm.[43]

Baseline heart rate, heart rate profile during exercise, and heart rate variability, at least in part, reflect the influences of the autonomic nervous system on cardiac rhythm. Decreased heart rate variability is characteristic of patients with more severe cardiac disease and at an increased risk of sudden death; it is typically associated with a reduction in parasympathetic (vagal) tone and thus either a relative or absolute increase in sympathetic tone (and heart rate). In healthy male (but not female) subjects, a 12-week regimen of dietary supplementation with 2.0 or 6.6 g/d n-3 PUFAs resulted in increased heart rate variability.[44] A positive correlation was observed between cell membrane DHA content and heart rate variability in men both at baseline and after treatment. The same group has reported similar treatment-related improve-

ments in heart rate variability in survivors of MI.[44] Although available data suggest a potential beneficial impact of n-3 fatty acid supplementation on heart rate variability, assessment of heart rate variability has thus far proven to be too crude to guide the treatment of individual patients. In contrast, estimates of microvolt-level T-wave alternans may have greater diagnostic utility for identifying individual patients at high risk of sudden death.[45] It will be of great interest to apply this technology to the evaluation of the efficacy of n-3 PUFA supplementation.

Intermediate-Chain n-3 Fatty Acids and Ventricular Arrhythmias

Observational Data

ALA is an intermediate-chain n-3 fatty acid found in high concentrations in flaxseed, soybean, and canola oils and other foods of plant origin. After ingestion, ALA is partly converted (≈4% to 8%) into the long-chain n-3 fatty acids found in fish (primarily EPA).[12] ALA has direct antiarrhythmic properties in animal models independent of its elongation into EPA,[46] and it has been hypothesized that ALA may have antiarrhythmic properties in humans. For several reasons, it would be useful to evaluate the antiarrhythmic efficacy of alternative sources of n-3 fatty acids such as ALA. First, fatty fish is neither readily available nor palatable to all populations. Second, even if fish could be made available to all populations, concerns exist that the supply of fish and fish oil supplements will be inadequate to meet recommendations without significantly depleting ocean fisheries.[47] Finally, certain types of fish have been documented to contain significant amounts of methyl mercury, polychlorinated biphenyls, dioxins, and other environmental contaminants.[48] Exposure to methyl mercury may have deleterious effects that could offset the benefit of long-chain n-3 fatty acids.[49] Although the risks associated with mercury and organochloride contamination can be eliminated by the use of carefully regulated, refined n-3 fatty acid supplements, investigation of alternative sources may provide a more readily available and less costly source of supplemental n-3 fatty acids.

A novel source of omega-3 fatty acids could come from the genetic manipulation of large mammals currently in the food chain. A humanized fat-1 gene (fatty acid desaturase) has been expressed in swine, potentially resulting in a novel source of omega-3–rich pork.[50]

It is possible, however, that the dietary source (animal versus vegetable) of ALA may be important. A meta-analysis by Brouwer and colleagues[51] contrasts the potential beneficial effects of ALA supplementation on cardiovascular disease with an apparent increased risk of prostate cancer.

Compared with the evidence for an antiarrhythmic benefit of long-chain n-3 fatty acids, the evidence for a direct benefit of ALA on arrhythmia risk is less developed, and the supporting data are largely epidemiological.[5] Inverse associations between intake of ALA and risk of fatal CHD have been observed in most prospective cohort studies[17,52–54] but not in a single smaller study.[55] To our knowledge, only 2 studies have specifically examined the association between ALA intake and SCD. In an updated report from the Health Professional Follow-up Study among 45 722 men, ALA intake was not significantly related to risk of SCD, although there was a suggestion that the risk may have been lower in those with very low intakes of the long-chain n-3 fatty acids (<100 mg/d).[30] In contrast, ALA intake was inversely associated with risk of SCD (P for trend=0.02) among 76 763 women participating in the Nurses' Health Study.[56] Compared with women in the lowest quintile of ALA intake, those in the highest 2 quintiles had a 38% to 40% lower SCD risk. This inverse relationship with ACD risk was linear and remained significant even among women with high intakes of long-chain n-3 fatty acids. Similar to prior epidemiological data reported for the long-chain n-3 fatty acids, the protective association was specific for SCD rather than general for CHD, supporting the hypothesis that ALA may influence cardiovascular risk through effects on arrhythmogenesis and fatal ventricular arrhythmias.

Randomized Trials

ALA supplements have not been studied adequately in any large-scale randomized trials. A large-scale primary prevention trial was conducted in the 1960s, which randomized 13 578 participants to an ALA supplement (linseed oil 10 mL/d; ALA 5.25 g/d) or placebo.[57] However, the follow-up period was only 12 months, too short of a duration to allow for a significant number of events to occur in a primary prevention population. With respect to dietary intervention trials, 3 trials have evaluated the impact of diets enriched with ALA. One randomized secondary prevention trial that evaluated the effect of a Mediterranean diet rich in ALA found a 76% risk reduction in a combined end point of nonfatal MI and cardiac death in the group assigned to the Mediterranean diet, despite no changes in serum lipids.[58,59] Levels of ALA were higher in the intervention group and were found to be the only fatty acid correlated with outcome.[59] Unfortunately, many other differences exist between the control and the ALA-enriched Mediterranean diet, making it impossible to ascribe the observed benefit to ALA alone. Currently, the Alpha-Omega Trial in the Netherlands is testing the effect of low-dose supplementation with omega-3 fatty acids (EPA+DHA [400 mg] with and without ALA [2 g]) delivered through specially prepared margarine on CHD mortality in patients who had a MI within the past 10 years. SCD is not a prespecified end point in this trial.

Fatty Acids and Atrial Fibrillation

Observational Studies

Epidemiological data examining the association between n-3 fatty acids and atrial arrhythmias are less developed than those described above for ventricular arrhythmias and SCD. Three prospective epidemiological investigations have been published, with conflicting conclusions. In 1 cohort study composed of 4815 men and women aged ≥65 years (mean age, 72.8 years), consumption of baked or broiled fish was associated with a reduced risk of developing atrial fibrillation (AF) over 12 years of follow-up.[60] Individuals with the highest intake of this type of fish experienced a 31% reduction in risk of new AF. In contrast, a second prospective cohort of 47 949 involving a much younger population (mean age, 56 years) found an increased incidence of AF associated

with increased fish consumption over 5.7 years of follow-up.[61] In this study, those with the highest intakes of long-chain n-3 fatty acids from fish had a 34% increased risk of developing AF. In the most recently published study, 5184 subjects free of AF at baseline were followed up for a mean follow-up of 6.4±1.6 years, and 312 subjects developed AF. No association was detected between (1) dietary consumption of >20 g fish per day (assessed by questionnaire) or (2) EPA/DHA intake (computed on the basis of a food composition database) and the risk of AF.[62] To our knowledge, no studies have yet examined the association between dietary ALA intake and AF.

Randomized Trials

In addition to these limited results from observational studies, results from a small, open-label randomized trial among 160 patients undergoing coronary artery bypass grafting have been published recently.[63] Patients were randomly assigned to therapy with 850 mg EPA/DHA (1:2) beginning 5 days before surgery and continuing until hospital discharge. Postoperative AF developed in 12 patients randomized to n-3 fatty acids (15.2%) compared with 27 patients randomized to the control group (33.3%) ($P=0.013$). Several small-scale randomized trials are under way that seek to examine the impact of n-3 fatty acid supplementation on episodes of paroxysmal AF or AF recurrence after cardioversion.

A plausible explanation for the divergent results observed in the observational studies of AF is the heterogeneity of AF subtypes across cohorts. In younger populations, it is estimated that 20% to 45% of AF is lone AF without associated comorbidities (such as diabetes and hypertension) or structural heart disease.[64] Because parasympathetic (vagal) activity has been linked to the onset of AF in patients with structurally normal hearts[65] and long-chain n-3 fatty acids may increase parasympathetic tone,[44] one could hypothesize that fatty acids may precipitate AF in younger patients. At the same time, in older patients with impaired vagal tone, the same fatty acids might be protective. In the older population, the incidence of AF is related to structural heart disease, systemic inflammation, atrial fibrosis, and impaired hemodynamics. AF in the postoperative setting is linked to a markedly elevated systemic inflammatory response subsequent to the surgical trauma,[66] leukocyte activation,[67] recovery from anesthesia, altered autonomic tone, and acute hemodynamic changes. Clearly, more research is required to elucidate the possible differences in the effects of n-3 fatty acids on AF that result from distinct underlying causes.

Recommendations for Future Epidemiological/Clinical Studies

Although the weight of the evidence from epidemiological and clinical trials supports the hypothesis that the long-chain n-3 fatty acids found in fish reduce risk of SCD, the results from ICD trials that have examined ventricular arrhythmias as the primary end point have not been consistent, with one trial raising the possibility that these n-3 fatty acids could be proarrhythmic under certain conditions, another showing a strong trend toward benefit using the primary end point of time to first ICD discharge for VT/VF, and the third showing a trend toward decreased VT/VF or death only in the subgroup of patients with a prior MI. In addition, to date, no large-scale randomized, double-blind trial has examined SCD or VT/VF as the primary end point. With respect to AF risk, the data for a benefit of these fatty acids are quite limited at this time, and the data for ALA influencing risk of SCD are equally sparse. Therefore, additional data are needed before these supplements can be recommended as antiarrhythmic agents. On the basis of the available data summarized above, the workshop members had the following recommendations for future epidemiological and clinical trials to further understanding regarding the possible antiarrhythmic actions of the n-3 fatty acids in humans.

- Further exploration and pooling of the data (eg, blood samples, electrogram recordings) from completed randomized trials in the ICD patient population in an attempt to better understand the divergent results on risk for VT/VF, with particular examination for heterogeneity to better understand which patient populations may benefit, are needed.
- Additional epidemiological data are needed on the association between ALA intake and SCD and/or cardiac arrest.
- Additional epidemiological studies that examine the association between dietary sources and blood levels of n-3 fatty acids (EPA, DHA, and ALA) and AF are warranted. These studies should specifically explore whether effects differ by type of AF so that more informed choices regarding selection of targeted patient populations for randomized trials can be made.
- On the basis of the available data, large-scale double-blind, randomized trials with well-defined SCD and/or VT/VF end points are justifiable among patients with a history of MI and/or among patients with systolic dysfunction.
- Small-scale randomized trials in well-defined AF populations, such as the post–coronary artery bypass graft population, are justifiable at this time.

Future randomized trials should feature the following:

- Patient selection and follow-up should include clinically relevant biological parameters and markers (eg, plasma and cellular n-3 fatty acid levels and markers of systemic inflammation, redox state, or oxidative stress).
- ALA supplements should be examined in addition to the long-chain n-3 fatty acids whenever feasible.
- For VT/VF end points in ICD patient populations, device programming should either be standardized or only shocks for ventricular arrhythmias with rapid rates should be included in the end point.
- The impact of n-3 PUFA supplementation on T-wave alternans should be examined.
- The data should be examined for evidence of both benefit and harm.
- Blood samples should be collected for future biomarker, genetic, and proteomic analyses.

Animal Models

Animal models allow the study of variables not easily accessible in human trials and can lead to a better understand-

Arrhythmia Studies in Animals With Dietary n-3 Fatty Acid Supplementation

Study (Year)	Dietary Supplement/Duration	Species	Model	Results
Leprán et al[70] (1981)	SC, SC+sunflower seed oil; 3 mo	Sprague-Dawley rats	Surgical MI in conscious rats	Significant reduction in VT/VF and mortality in sunflower seed oil–fed rats
Charnock et al[71] (1985)	SC, SC+sheep kidney fat, SC +sunflower seed oil; 4 and 15 mo	Hooded Wistar rats	Isolated papillary muscles±isoproterenol	Significant reduction in isoproterenol-induced arrhythmias in sunflower seed oil– vs sheep kidney fat–fed rats at 4 and 15 mo
McLennan et al[72] (1985)	SC, SC+sunflower seed oil (linoleic rich), SC+sheep kidney fat (linoleic poor); 7 and 20 mo	Male Wistar rats	Surgical MI	Significant reduction in VT/VF duration at 7 and 20 mo and reduction in PVCs and AS at 20 mo in sunflower seed oil–fed rats
Hock et al[73] (1990)	SC+corn oil, SC+menhaden oil; 4 wk	Weanling Sprague-Dawley rats	Surgical ischemia/reperfusion	Significant survival benefit and reduced VT/VF and AS in menhaden-fed rats
McLennan et al[74] (1992)	SC, SC+tuna fish oil, SC+sunflower seed oil, SC+saturated fat; 30 mo	Marmoset monkeys	Reversible surgical ischemia, isoproterenol, and PES	Significant reduction in VF induction in tuna fish oil– and sunflower seed oil–fed animals; no deaths in tuna fish oil–fed animals
McLennan et al[75] (1993)	SC+olive oil, SC+sheep kidney fat, SC+sunflower seed oil, SC+fish oil; 12 wk	Sprague-Dawley rats	Reversible surgical ischemia	Significant reduction in mortality in sunflower seed oil and fish oil groups
Yang et al[76] (1993)	SC+fish oil, SC+butter fat; 5 d	Sprague-Dawley rats	Ex vivo, blood-perfused working hearts±ischemia/reperfusion injury	Significant resistance to reperfusion VT/VF in fish oil–fed rats and improved mechanical recovery
Kinoshita 1994[77]	SC, SC+EPA (100 mg/kg per day); 8 wk	Mongrel dogs	Surgical MI±digoxin (0.025 mg/kg)	Significant reduction in PVC and AS but not VF; significant increase in n-3/n-6 in heart and platelets in EPA group; increased SERCA activity in EPA group
Anderson et al[78] (1996)	SC, SC+coconut oil, SC+fish oil, SC+safflower oil; 8 wk	Sprague-Dawley rats	In situ perfused hearts±ischemia/reperfusion injury	Significant reduction in VT/VF and AS in fish oil–fed rats
Liefert et al[79] (2001)	SC+fish oil, SC+saturated fat; 3 wk	Sprague-Dawley rats	Paced isolated ventricular myocytes	Myocytes from fish oil–fed rats were resistant to isoproterenol-induced asynchrony; no differences in SR Ca^{2+} content or membrane fluidity
Pepe et al[80] (2002)	SC, SC+fish oil, SC+saturated fat; 16 wk	Wistar rats	Ex vivo, blood-perfused working hearts±ischemia/reperfusion injury	Significant resistance to reperfusion VF and increased metabolic efficiency in fish oil–fed hearts

SC indicates standard chow; PES, programmed electric stimulation; PVC, premature ventricular contraction; AS, arrhythmia score; and SERCA, sarcoplasmic-endoplasmic reticulum calcium ATPase.

ing of the mechanisms. Animal studies of n-3 PUFAs have consisted largely of long-term dietary manipulations and short-term intravenous exposure.[68,69]

Dietary Supplementation in Rodent and Large-Animal Models

As previously discussed, dietary intervention and observational studies have suggested that dietary supplementation with n-3 PUFAs can reduce mortality in humans and that suppression of SCD is a potential mechanism for these beneficial actions.[31,35,36] Experiments using animal models of dietary supplementation with fatty acids support these findings (Table).[70-80] Rats fed n-3 fatty acids from fish or plant sources and subjected to surgical MIs, reversible surgical ischemia, or ischemia/reperfusion showed survival benefit and decreased arrhythmias.[70,72,73,75,78] Similarly, isolated

hearts, papillary muscles, and myocytes from the hearts of rats fed n-3 PUFAs showed improved recovery from ischemic insults, resistance to arrhythmias, and evidence of decreased calcium overload.[71,76,79,80] Studies on large-animal models are more limited. Dogs treated with EPA (100 mg/kg per day for 8 weeks) showed a reduction in arrhythmias after coronary ligation,[77] and Marmoset monkeys treated with tuna fish oil or sunflower seed oil showed fewer inducible arrhythmias in the setting of reversible surgical ischemia and isoproterenol.[74] Taken together, these findings appear to support the benefits of n-3 fatty acids and their potential role in arrhythmia prevention, although well-controlled studies in large-animal models relevant to human sudden death are limited.

Findings in animals that dietary n-3 fatty acid supplementation can reduce adrenoreceptor responsiveness[81,82] and inhibit the activity of calmodulin kinase II and protein kinase A[83–85] are consistent with the observation that dietary fish oil supplementation reduces heart rate in humans.[43,86] In contrast to human studies, dietary studies in rodents and nonrodents[87] have thus far failed to mirror this heart rate reduction with fish- or plant-derived n-3 fatty acids (Table). This apparent difference between heart rate responses to dietary n-3 fatty acids in humans and animal models may indicate that antiarrhythmic actions are fundamentally different in humans and other animals (even small primates) or that heart rate responses are distinct from antiarrhythmic effects of dietary n-3 fatty acids. Longer monitoring of heart rates in animal models (eg, with implanted ECG telemeters) or more studies with larger animals with slower, more humanlike heart rate responses may be required to resolve this question.

Short-Term Antiarrhythmic Effects of Intravenous n-3 Fatty Acids

Intravenous fish oil extract, DHA, EPA, and ALA were all effective in reducing VF in a dog model of exercise-induced adrenergic stress and myocardial ischemia.[46,88] These findings are important because they established the efficacy of fish- and plant-derived n-3 fatty acids in suppressing an arrhythmia clearly linked to SCD in a nonrodent model. These findings also show that antiarrhythmic properties of n-3 fatty acids are evident with short-term administration, support a preliminary study in humans that showed fewer inducible arrhythmias in ICD patients treated for a short period with 3.8 g of n-3 PUFAs,[89] and could provide a conceptual link to most of the cellular and molecular studies that have focused largely on immediate responses to these agents.

The effect of short-term administration of n-3 PUFAs on electric remodeling of the dog atrium has also been examined.[90] The decrease in atrial effective refractory period after rapid atrial pacing was attenuated by n-3 but not by n-6 PUFAs, suggesting that n-3 PUFAs may help to minimize the self-perpetuation of AF.

Recommendations for Future Animal Studies

Animal models are the only available approach for measuring and vertically integrating arrhythmia mechanisms from molecules to biological systems. All studies to date indicate that dietary supplementation is effective for suppressing arrhythmias in rodents and nonrodents, suggesting that both rodent and nonrodent models will be useful for determining mechanisms for arrhythmia suppression by n-3 fatty acids. An important goal will be to ascertain which antiarrhythmic mechanisms are most important in dietary n-3 fatty acid supplementation because dietary supplementation is the most applicable route of administration for potential future public health initiatives to reduce SCD. It will also be necessary to establish the efficacy of plant-derived n-3 fatty acids compared with fish oil because plant sources of n-3 fatty acids could be less expensive and are not limited by concerns about heavy metal contaminants or depletion of endangered fisheries.

It will be important to do the following:

- Systematically determine the most effective dietary agents (fish oil versus plant) and regimens (dose and time) for arrhythmia suppression, along with the effects of these regimens on tissue proportions of n-3 and n-6 fatty acids.
- Determine the relationship between arrhythmia suppression and diet-induced changes in membrane lipid characteristics.
- Selectively use animal models for answering specific questions. For example, genetically modified animals (mostly rodents) may be most appropriate for determining specific molecular mechanisms for n-3 PUFA actions. On the other hand, larger-animal (nonrodent) models will likely be advantageous for modeling tissue and heart rate effects of n-3 PUFAs.
- Use multiple modern approaches to understand cellular (voltage clamp, current clamp, Ca^{2+}_i, and oxidant reporters), molecular (transgenic and knockout models), in situ (mapping), and in vivo (telemetry, programmed stimulation, molecular imaging) arrhythmia mechanisms.
- Apply proteomic, lipidomic, and genomic analysis to hearts and cardiomyocytes from animals fed with n-3 fatty acids to determine global responses to these dietary interventions.

Cellular Mechanisms

Direct Membrane Effects

Dietary supplementation causes a reordering of lipid membranes with enhancement of resident n-3 fatty acid components[70,73,75,77,78,91] and reduction in thromboxane B_2.[76] These changes have not been shown to occur in response to short-term, intravenous administration of n-3 fatty acids.[46] Dietary supplementation of rats with 10% fish oil can double the content of DHA in myocardial membranes after 2 days, whereas myocardial EPA accumulation is lower.[91] Dietary supplementation of rats with n-3 fatty acids for periods as short as 5 days can reorder the content of peripheral and myocardial lipid pools and reduce arrhythmia susceptibility.[76] These changes in n-3 fatty acid may have profound effects on trafficking of ion channels through subcellular compartments and in lipid rafts.[92] It will be important to establish whether changes in membrane lipid constituents are part of the antiarrhythmic mechanism for n-3 fatty acids and whether dietary and parenteral n-3 fatty acid supplementation act by

similar mechanisms. It will also be important to directly measure changes in tissue PUFAs in response to dietary supplementation in future animal trials.

Ion Channels and Exchangers

Evidence from clinical observations and animal models published within the last decade provide consistent, although still only suggestive, evidence that ion channel–mediated effects of PUFAs can have antiarrhythmic effects.[46,86,93] These effects may be mediated at least in part through actions on the Na^+ channel, which underlie the excitation of myocytes in the ventricular myocardium. As noted above, the data from clinical trials are somewhat inconsistent and at times conflicting. Similarly, a detailed study of the dose dependence of the PUFAs (EPA and DHA) in guinea pig and rat ventricular myocytes revealed complex findings that were interpreted in terms of species dependence and/or superfusate/plasma levels of the PUFA.[94] Thus, in the rat heart at low concentrations, DHA caused an increased plateau height, lengthening of the action potential duration, and a positive inotropic effect. In contrast, at higher concentrations in the rat myocardium (and at all levels that were tested in the guinea pig myocardium), these same agents reduced excitability and contractility. Interspecies differences in cardiac ion channel distribution might account for the differences in response to exogenous fatty acids. Accordingly, a careful examination of the ionic mechanisms of the actions of PUFAs in mammalian myocardium is needed.

Sodium Channels

The effects of DHA and EPA on Na^+ currents in a number of different isolated mammalian myocyte preparations (including neonatal and adult rat ventricular myocytes) have been studied extensively.[95,96] The effects of PUFAs on cardiac Na^+ channels have also been studied with the use of heterologous expression systems based on either *Xenopus* oocytes or mammalian HEK cells.[97–99] Collectively, these findings show significant dose-dependent inhibition of Na^+ current at PUFA concentrations similar to those that have been measured in plasma in human trials or animal studies that demonstrate protection against arrhythmias or sudden death.[46,93] Coexpression of sodium channels with the appropriate β-subunits can modify the effects of PUFAs on the Na^+ current,[99] and the so-called persistent or noninactivating component of the Na^+ current may be preferentially altered.[95] In addition, heterologous expression experiments using Na^+ channels with single-point mutations have identified regions of interactions of DHA with $Na_v1.5$.[97]

The possibility that some of these PUFA effects in mammalian heart could be targeted to a specific component of the Na^+ channel kinetic scheme (ie, slow inactivation) is of interest. Additional examination of this possibility requires knowledge of the expression levels of the β-subunits that interact with $Na_v1.5$ in the mammalian ventricle.[100–105] The data demonstrating a significant alteration in PUFA effects on $Na_v1.5$ after selected point mutations provide strong evidence that the primary effect is localized to the α-subunit. However, the well-known ability of β-subunits to (1) alter voltage dependence of activation and inactivation, (2) change sarcolemmal expression levels, and/or (3) contribute to the interactions of the sodium channels with the extracellular matrix in mammalian heart needs to be considered in experimental design and in the interpretation of available in vitro and in vivo data.[106] In addition, possible PUFA-mediated changes in G-protein regulation of sodium channel function should be considered.[107] Furthermore, the possibility that PUFA-induced changes in the Na^+ current could alter Na^+ homeostasis in the myocyte and thus indirectly change pH regulation, contractility, or diastolic excitability needs to be evaluated.

Potassium Channels

Both DHA and EPA can inhibit a number of different K^+ currents at concentrations very similar to those that interact with and block sodium channels, and this effect may contribute to reports of cardiovascular protection.[108,109] Kv1.5, the channel responsible for the I_{Kur} current, provides a significant fraction of the repolarizing current in human atrium and is significantly inhibited by PUFAs.[110–112] Whereas Kv1.5 protein is ubiquitously expressed in atrial and ventricular myocardium, the corresponding I_{Kur} current is restricted to atrial myocytes in larger mammals; in mice, I_{Kur} is present in both ventricular and atrial myocytes.[113] Inhibitory effects of DHA on Kv1.1 and Kv1.2 channels have also been reported.[114,115] More recent findings report significant inhibitory effects of DHA on the Kv4 family of K^+ channels that are responsible for the transient outward current, which initiates early repolarization in mammalian hearts at concentrations of $\approx$5 μmol/L.[116] Interestingly, the inhibitory effect may involve, or even require, prior peroxidation and suggests that the redox environment within the myocardium may modulate some of the electrophysiological effects of PUFAs.[117]

The ability of PUFAs to inhibit K^+ currents generated by Kv1.5, Kv4.2, and/or Kv4.3 could provide a plausible reason for the species- and concentration-dependent effects on the action potential and contractility.[94] At low concentrations, PUFAs could increase action potential height and result in a positive inotropic effect in rat ventricle. Important interactions between the calcium-independent transient outward potassium current (I_{to}) and the L-type calcium currents, with resulting inotropic effects in rat heart, have been described in detail.[118–120] Somewhat similar mechanisms may explain the complex alterations in early repolarization or in the action potential upstroke after alteration of I_{to}.[121] It is possible, therefore, that changes in K^+ currents due to PUFAs could lead to hemodynamic effects in humans.[122,123]

Calcium Channels

The major pathway for Ca^{2+} influx into cardiomyocytes is through L-type Ca^{2+} channels. There is agreement from short-term studies that n-3 fatty acids reduce peak I_{Ca}, suggesting that a reduction in cellular Ca^{2+} entry may contribute to the Ca^{2+} antagonist actions.[124–129] T-type Ca^{2+} channels also serve as a point of Ca^{2+} entry for atrial cardiomyocytes and for specialized conduction cells, and short-term application of DHA, EPA, or ALA can reduce T-type Ca^{2+} entry in adrenal glomerulosa cells.[130] We are aware of no studies to test the effects of dietary n-3 fatty acid supplementation on L- or T-type Ca^{2+} channel function or expression. Lack of data on Ca^{2+} entry in dietary models is a

significant knowledge gap. For example, the mechanism for inhibition of peak Na^+ current (I_{Na}) by short-term addition of EPA and DHA may be due, at least in part, to changes in cell membrane fluidity because other detergents produce similar effects[131] and because direct measurements show that membrane fluidity is significantly enhanced by short-term addition of n-3 fatty acids to cultured cells.[132] In contrast, membrane fluidity may not be affected by dietary n-3 fatty acid supplementation.[79] Short-term addition of DHA reduces the efficacy of dihydropyridine agonist and antagonist agents,[128] but cardiomyocytes isolated from rats fed a fish oil–supplemented diet do not show a difference in response to the I_{Ca} agonist drug BAYK8644.[79] These discrepancies suggest fundamental differences in antiarrhythmic mechanisms from short-term and long-term (dietary) supplementation from n-3 fatty acids.

Other Sarcolemmal Ion Channels

PUFA compounds may, at similar doses, affect ATP-dependent K^+ currents and some transcripts in the TRP family of ion channels. A significant inhibition of $I_{K\text{-}ATP}$ in neurons from the mammalian hypothalamus has been reported.[133] At present, no reports exist of any analogous effects on $I_{K\text{-}ATP}$ in heart. Effects of PUFA compounds on TRP channels include an inhibition of TRP-V–mediated current in invertebrate neurons.[134,135] Because somewhat analogous channels are expressed in sensory nerves, perhaps within mammalian heart, this observation could have physiological and/or pathophysiological relevance.

Sarcoplasmic Reticulum Ca^{2+} Release Channel

EPA can suppress arrhythmias in a canine model of ischemia and cellular Ca^{2+} overload due to digoxin toxicity.[77] These findings are consistent with other results in vivo[136] and in isolated cardiac myocytes that suggest that a significant aspect of n-3 fatty acid antiarrhythmic activity is linked to prevention of cellular Ca^{2+} overload. The sarcoplasmic reticulum (SR) is the source of most cellular Ca^{2+} that directly activates myofilaments.[137] SR Ca^{2+} release can be disordered to cause mechanical dyssynchrony and arrhythmias due to overfilling or to defects in the SR Ca^{2+} release (ryanodine receptor) channel. Some mechanical responses to n-3 fatty acids may be species dependent. For example, isolated rat ventricular myocytes show a transient increase in contraction followed by a more sustained decrease, whereas guinea pig ventricular myocytes exhibit a monotonic decrease in contraction amplitude after short-term application of EPA.[129] Short-term application of n-3 fatty acids causes an increase in SR Ca^{2+} content[126] and a reduction in ryanodine receptor openings.[138,139] In contrast, dietary n-3 fatty acid supplementation may not increase SR Ca^{2+} content.[79] Intracellular Ca^{2+} "waves" represent propagated release of SR Ca^{2+} and are an underlying focal mechanism for arrhythmia initiation. Short-term[126,131,132,140] and long-term (dietary)[79] n-3 fatty acid supplementation both suppress the frequency of Ca^{2+} waves and can reduce dyssynchronous beating in response to isoproterenol. The apparent difference in the effects of short-term and long-term n-3 fatty acid supplementation on SR Ca^{2+} suggests that different cellular mechanisms may be responsible for Ca^{2+} wave suppression by short-term and long-term (dietary) n-3 fatty acid supplementation.

Sodium–Calcium Exchanger

In its forward mode, the sodium-calcium exchanger (NCX) provides a mechanism for extruding calcium from the cytosol and facilitates diastolic relaxation between cycles of cardiac excitation. Reverse-mode NCX activity occurs early in the action potential and can facilitate calcium influx. The importance of the NCX is somewhat variable between species, accounting for ≈30% of Ca^{2+} extrusion during diastole in rabbit ventricle compared with ≈10% in rat, a difference that likely reflects underlying species differences in the regulation of cytosolic $[Na^+]$.[141] NCX protein expression is often increased in the ventricle of patients with end-stage heart failure[142] and in the atria of patients with AF,[143] perhaps as a means of compensating for other Ca^{2+} cycling abnormalities. A study in pigs has reported that dietary supplementation with n-3 fatty acids resulted in a 60% reduction in NCX current.[144] Modulation of NCX activity in the diseased heart may contribute to the antiarrhythmic efficacy of n-3 fatty acids.

Connexins

Results published >10 years ago demonstrated significant, structure-specific effects of free fatty acids on the connexon-mediated communication between rat ventricular myocytes.[145] Some of these effects are attributable to free fatty acids, which differ significantly from the n-3 PUFAs that are the focus of this review. Nevertheless, both DHA and EPA can act as significant inhibitors of intercellular communication in mammalian heart. This finding, as well as the effects of PUFAs to inhibit Na^+ currents in myocytes, has been integrated with the use of mathematical models of the membrane action potentials in mammalian heart. These simulations were aimed at determining the relative importance of inhibition of Na^+ current versus block of connexon-mediated intracellular communication in mammalian ventricle and demonstrate the potential of computational biology to integrate experimental findings and plan new experiments in this field.[146–148]

Protein Kinases

In animals, dietary n-3 fatty acid supplementation can reduce β-adrenergic receptor responsiveness[81,82,149] and inhibit the activity of protein kinase A and calmodulin kinase II.[83,84] Protein kinase A is the major mediator of β-adrenergic signaling, plays an important role in ion channel modulation, and is clearly linked to sudden death in humans.[150] Calmodulin kinase II, meanwhile, has been shown to play an important role in arrhythmia susceptibility in mice and rabbits.[85,151]

Inflammatory Mediators

Omega-6–Derived metabolites including thromboxane A_2 and prostaglandin $F_{2\alpha}$ have been implicated in the genesis of tachycardias associated with systemic inflammation.[152] n-3 fatty acids from multiple sources appear to be effective in increasing n-3 fatty acids in myocardial membranes, reducing production of proinflammatory thromboxanes, and suppress-

ing arrhythmias. In the setting of ischemia, phospholipase A_2 is activated, stimulating the production of additional arachidonate-derived metabolites including platelet activating factor. These mediators have been implicated in ischemia-mediated SCD.[153] A dietary (and cell membrane) shift in the balance of n-3 to n-6 fatty acids might attenuate the production of proarrhythmic lipids. DHA can reduce inflammatory signaling associated with increased cellular Ca^{2+} and activation of nuclear factor-κB in neutrophils.[154] Activation of nuclear factor-κB in neutrophils by intracellular Ca^{2+}-dependent mechanisms also provides a potential rationale for linking Ca^{2+} inhibitory and anti-inflammatory properties of n-3 fatty acids in vivo.[154,155]

Relationship to Clinical Arrhythmias

Lethal arrhythmias usually require both a trigger and a substrate that contribute to initiation and persistence. Early and delayed afterdepolarizations are implicated as important mechanisms underlying the abnormal automaticity that triggers many arrhythmic episodes. In experimental studies, different cellular mechanisms have been linked to these arrhythmic triggers. Early afterdepolarizations typically occur at slow heart rates and accompany interventions that promote action potential prolongation. Early afterdepolarizations have been attributed in part to recovery of the L-type calcium current late in the action potential. Suppression of calmodulin kinase II activity can attenuate early afterdepolarization formation in a rabbit heart model in which early afterdepolarization formation is enhanced by K^+ channel blockade.[151] Suppression of calcium currents and/or calmodulin kinase II by n-3 fatty acids might contribute to a reduction in the frequency of early afterdepolarizations. In contrast, delayed afterdepolarizations are generated by spontaneous release of calcium from the SR. Increased NCX activity is believed to contribute to the occurrence of delayed afterdepolarizations, and these can trigger arrhythmic events.[144] Spontaneous calcium release is also modulated by the calcium load of the SR and by the redox state of the myocardium. Thus, delayed afterdepolarizations are facilitated by increased heart rate, which can lead to increased cellular sodium levels (promoting reverse-mode NCX-mediated calcium influx) and increased SR calcium loading. A reduction of NCX currents by n-3 fatty acids might be anticipated to attenuate delayed afterdepolarization formation.

n-3 fatty acids also alter ion channels and intercellular coupling, and these may affect reentry circuits and the likelihood of reentrant ventricular tachycardia to degenerate into ventricular fibrillation. Of note, substances (including omega-3 supplements) that directly modulate cardiac ion channels, exchangers, or other elements of excitability may simultaneously have the potential for proarrhythmia.[144] Thus, whereas abbreviating action potential duration can diminish the likelihood of EAD formation, n-3 fatty acids could also promote reentrant arrhythmias.

Recommendations for Future Mechanistic Studies

It is now clear that a number of different n-3 PUFAs can influence cardiac ion channel activity at concentrations near those measured in plasma. In a general sense, these studies have validated the concept that n-3 fatty acids suppress mechanical responses and reduce surrogate markers of arrhythmia driven by cellular Ca^{2+} overload. However, the relationships of these studies to studies with dietary n-3 fatty acid supplementation remain uncertain. Most studies of isolated ventricular myocytes have involved short-term addition of micromolar levels of n-3 fatty acids to the superfusate (but see the Table[79]). High concentrations of free n-3 fatty acids are unlikely to reflect n-3 fatty acid activity after dietary supplementation, in which only a miniscule fraction of n-3 fatty acid is unbound. Another factor that must be considered is that most studies have been performed in the setting of normal cardiac function, whereas in the setting of postinfarction in mammalian ventricle, the voltage dependence and kinetics of Na^+ currents are altered substantially.[63,156] Biophysical and pharmacological properties of the Na^+ current may differ in the atria versus ventricles of the same mammalian heart, and computational studies have suggested that Na^+ current inhibition may be able to reduce AF.[157–159]

In future studies, it will be important to do the following:

- Determine whether and to what extent these agents may exhibit selective effects on the excitability, action potential waveform, or inotropic status of mammalian atria and ventricles and the conduction system including Purkinje cells.
- Study the effects of n-3 PUFAs on the early and late phases of repolarization, which may be modulated by noninactivating Na^+ currents, a declining L-type calcium current, I_{to}, other delayed rectifier K^+ currents, the NCX, and Na^+/H^+ ion exchange.[160–164] In the atrium, specific attention should be given to the K^+ channel Kv1.5.
- Carefully consider new experimental models and solutions that can mimic global ischemia.[165]
- Replicate changes in the redox environment that may lead to changes in inflammatory markers in cardiovascular disease, along with mimicking potential free radical challenge.[166,167]
- Understand the relationship of PUFA supplementation to proarrhythmic cellular signaling pathways.

Summary

Cardiac electric activity is strongly modulated by its environment. Factors modulating this activity include the metabolic state of the myocyte, the availability of oxygen and energy substrates (including plasma fatty acids and glucose), mechanical forces, autonomic tone, and the lipid composition of the cell membrane. Ion channels, exchangers, and pumps act as macromolecular complexes and are regulated by phosphorylation, prenylation, and numerous other signaling pathways.

Contemporary changes in diet (including increased caloric content, increased consumption of glucose and omega-6 fatty acids, decreased consumption of omega-3 fatty acids) and an overall decrease in exercise and activity have contributed to an increased incidence of obesity and diabetes in the adult and pediatric population. These trends, in turn, have led to an increased incidence of cardiovascular diseases including atherosclerosis, AF, and congestive heart failure, each of which

is associated with increased risk of mortality. SCD due to arrhythmias is a primary cause of increased mortality.

Efforts to better understand the links between diet and cardiac rhythm have the potential to improve public health and welfare and to reduce the ballooning costs associated with treating cardiovascular disease. That omega-3 fatty acids have an impact on the fundamental elements (ion channels, exchangers, and modulators) of cardiac electric activity is now indisputable. However, the translation of this understanding into evidence-based public policy guidelines that can decrease the incidence of arrhythmias and SCD still requires significant additional efforts. In this review we have identified a number of concrete areas for investigation that will help to provide some of the information that is required to best meet this goal.

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KEY WORDS: arrhythmia ■ death, sudden ■ diet ■ electrophysiology ■ fatty acids

Omega-3 Fatty Acids and Cardiac Arrhythmias: Prior Studies and Recommendations for Future Research: A Report from the National Heart, Lung, and Blood Institute and Office of Dietary Supplements Omega-3 Fatty Acids and Their Role in Cardiac Arrhythmogenesis Workshop

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