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Omega-3 Fatty Acids, Ventricular Arrhythmias, and Sudden Cardiac Death: Antiarrhythmic, Proarrhythmic or Neither

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A substantial body of evidence from observational studies, experimental models, and clinical trials has accumulated over the past 30 years in support of the hypothesis that increasing intake of long chain n-3 polyunsaturated fatty acids (PUFAs) from fish may protect against lethal ventricular arrhythmias in the setting of CHD[1]. Beginning in the 1980s, these fatty acids were documented to confer protection against ventricular fibrillation in the setting of ischemia in animal models[2-5] and experimental studies subsequently uncovered plausible electrophysiologic mechanisms to explain these antiarrhythmic effects, including modulation of ion channels and the autonomic nervous system[1, 6] The study by Billman et al in this issue of Circulation, Arrhythmia and Electrophysiology[7] sent out to confirm these antiarrhythmic effects in a canine post myocardial infarction model of SCD; however, the results were not as expected.

In two independent laboratories, dietary supplementation with n-3 PUFAs did not protect against ventricular arrhythmias. The first laboratory did not find suppression of ischemia-mediated ventricular fibrillation (VF) in 8 VF susceptible dogs after eight weeks of n-3 PUFA at a dose of 1 gram/day. The second laboratory utilized a more complicated dose ranging protocol with n-3 PUFA doses of 1, 2, and 4 grams as well as a corn oil placebo. There was a fairly high rate of unexpected spontaneous death (19%) in both the active and placebo treatment arms in dogs who exhibited exercise induced VF, which was not seen in the first laboratory nor in prior work examining intravenous n-3 PUFAs in the same animal model [4, 5]. These deaths were considered to be arrhythmic events, but continuous ECG monitoring was not performed so the mechanism remains uncertain. The outcome in the second study was an arrhythmia severity score, which incorporated these spontaneous deaths by assigning the highest score to these events. The score also included non-life-threatening arrhythmias such as PVCs and nonsustained VT as well as the endpoint of exercise-induced VF utilized in the prior study. Treatment with n-3 PUFAs or placebo did not reduce the arrhythmia score in VF susceptible dogs as initially hypothesized.

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In addition to a lack of a demonstrable antiarrhythmic effect in high risk animals, a possible proarrhythmic effect was observed in lower risk animals. Dogs which did not previously exhibit exercise-induced VF had a higher incidence of arrhythmias after treatment with n-3 PUFA as compared to placebo, with three dogs experiencing VF with exercise in the highest dosing category (4 grams). Two spontaneous deaths were also observed in sham dogs treated with 4 grams of n-3 fatty acids. Although there was no control group, such spontaneous deaths in this model had not previously been reported. The authors conclude from these data that dietary supplementation with n-3 PUFA significantly increases the susceptibility to malignant arrhythmias in these dogs.

The above findings are in direct contrast with those of a prior study by some of the same authors using intravenous rather than dietary administration of n-3 PUFA in the same canine SCD model[4, 5]. Although the prior study did not specifically test for a proarrhythmic effect in VF resistant dogs, intravenous infusions of n-3 PUFA were found to confer strong protection against VF in VF susceptible dogs[4, 5], which was clearly not demonstrated with dietary supplementation in either of the present studies. Although no direct mechanism is provided to explain these disparate findings, these data raise the possibility that the mode of administration of n-3 PUFA and/or the total accumulated dose might influence the summation of electrophysiologic actions. In experimental models, n-3 PUFAs have differing effects on repolarization, action potential duration, sodium channel blockade, and intracellular calcium handling depending upon whether the fatty acids are circulating (intravenous administration) or incorporated into cell membranes (dietary administration)[8]. It is also notable that majority of the potential pro-arrhythmic events were observed at the highest 4 gram dose. Although the authors state that all three doses had similar effects on the susceptibility to VF, this is difficult to critically evaluate given the small number of dogs in each dosing category and limited number of hard events. Therefore, the possibility that the electrophysiologic properties of n-3 PUFAs may differ at high versus low doses cannot be excluded.

It is important to emphasize that the findings regarding proarrhythmia are based upon very small numbers of animals and events, and as a result are of marginal statistical significance (P=0.044). Therefore, chance cannot be entirely excluded as a possible explanation for the findings. In addition, this work needs to be placed in the context of prior animal studies, which for the most part, have reported either protective or null effects on ventricular arrhythmias with n-3 PUFA dietary supplementation[9]. However, this study is not entirely in isolation either[8, 10]. There are other experimental studies which support the concept that n-3 PUFAs, similar to traditional antiarrhythmic drugs, may facilitate ventricular arrhythmias under certain conditions.[8] The question remains as to how these experimental data might translate to humans. What is the evidence from human studies that these fatty acids can precipitate ventricular arrhythmias?

Similar to the animal data, the majority of studies in humans suggest either protective or a null effect of dietary or supplemental intake of on n-3 PUFA ventricular arrhythmias or SCD. The data in support of an antiarrhythmic effect in humans is primarily derived from observational studies[11-14] and early randomized trials[1516] which reported protective associations with SCD that were stronger than that observed for other cardiovascular disease endpoints. In primarily healthy populations, consuming fish ~1-2 times per week (~200 mg n-3 PUFA) has been associated with significant 42-50% reductions in SCD risk in four separate studies.[11-14]. In two of these populations, individuals in the highest quartile of n-3 PUFA blood level were found to have 81-90% reductions in SCD risk as compared to those in the lowest quartile[14, 17]. In the GISSI Prevenzione trial, a supplement of 850mg n-3 PUFA lowered SCD risk in a large open label randomized trial among 11,324 post-MI patients[16]. The patients assigned to n-3 PUFA had a significant 15% reduction in the

primary endpoint (death, non-fatal MI, and non-fatal stroke), primarily due to a statistically significant reduction in SCD (45%) without any benefit on non-fatal MI or stroke.[18] Total mortality was significantly lower after 3 months of treatment, and the reduction in risk of SCD was already statistically significant at 4 months (RR 0.47; P=0.048).[18]

However, not all human data on n-3 PUFAs are supportive of these postulated antiarrhythmic properties and there are a couple of studies that do raise concerns regarding the potential for proarrhythmia. The DART-2 trial, which was conducted among 3,114 men with self-reported "chronic angina," found a paradoxical 26% higher risk of cardiac death and a 54% increased risk of SCD among men randomly assigned to advice to take up to 3 grams of fish oil or consume two portions of oily fish per week.[19] However, total mortality was not increased. This trial had some design issues including an interruption of the study for one year due to inadequate funds requiring re-randomization of participants, and follow-up of participants through a central register in the second phase of the trial. The elevated risk of SCD was only seen in the second phase of the trial primarily among those advised to take fish oil. It is unclear how these design issues might have influenced other dietary patterns, lifestyle habits, lost to follow-up rates, and SCD confirmation; but it is likely to have had some impact on the validity of the results.

The second study which raised concerns regarding proarrhythmia was performed among patients with implantable cardioverter defibrillators (ICDs) who had a prior history of VT/VF. Three randomized trials were carried out in this patient population at high risk for recurrent ventricular arrhythmias as a "proof of concept" that n-3 PUFAs protect against SCD through antiarrhythmic effects and suppression of VT/VF. All three trials failed to show a significant effect of n-3 PUFA supplementation on the risk of ICD therapy for ventricular arrhythmias.[20-22] While one trial found a trend towards an overall reduction in device therapy for ventricular arrhythmias[21]; another unexpectedly raised the possibility of proarrhythmia among a specific subgroup of patients[20]. The latter study by Raitt et al[20] found an unexpected increase in the risk of ICD therapy for ventricular arrhythmias with 1.8 grams of n-3 PUFA supplementation among a sub-group of patients whose qualifying arrhythmia was VT, where fixed scar reentry rather than ischemia might be expected to predominate as a mechanism. As with any subgroup finding, one must be cautious not to over interpret the finding, which could be due to chance. In addition, it has since become well recognized that an ICD therapy for ventricular arrhythmia does not equate with SCD in randomized trials,[23, 24] and such trials in ICD patients cannot substitute for those with SCD and total mortality endpoints.

There have since been 4 randomized trials of n-3 PUFAs that have examined SCD and total mortality as endpoints. All have been unable to replicate the initially promising results of the GISSI Prevenzione trial[16]. Two randomized trials performed in post-MI populations failed to demonstrate a benefit on SCD or CHD mortality in the modern era of pharmacotherapy [25, 26]. These trials were smaller and the SCD rate was much lower than had been observed in GISSI Prevenzione trial[16]. As a result these trials were significantly underpowered to detect even moderate-to-large reductions in SCD. The larger of the two trials, the Alpha Omega Trial, also used a lower dose (400 mg) of n-3 PUFA and included other events such as ICD implantation in the ventricular arrhythmic event endpoint[25]. Another trial performed among 18,645 hypercholesterolemic Japanese patients treated with statins[27] only documented 44 SCD events over a mean follow-up of 4.6 years. The only trial which was adequately powered to detect a clinically meaningful reduction in SCD was the recent GISSI-HF trial[28]. The study population was a heterogeneous heart failure population, which differed from prior trial populations in that only 50% of participants had underlying CHD. Patients randomized to n-3 PUFA had a marginally significant reduction in total mortality, a non-significant reduction in arrhythmic death, and a significantly lower rate of

hospitalizations for ventricular arrhythmia. None of the above trials reported any data to suggest that n-3 PUFAs were proarrhythmic in these populations.

So where do we stand regarding recommendations for n-3 PUFAs? Based upon the data available in 2002, AHA recommended that patients without documented CHD eat a variety of fish, preferably oily fish, at least twice a week. Patients with documented CHD are advised to consume approximately 1 g of EPA+DHA per day, preferably from oily fish[29], although EPA+DHA supplements could be considered in consultation with their physician. Does the present study along with the accumulated experimental and human evidence present significant cause for concern regarding the safety of these recommendations? At present, it does not appear to be so. There are little data to question the safety of the modest amounts of fish consumption recommended, and the preponderance of the evidence does not support a clinically detectable pro-arrhythmic effect associated with dosages of n-3 PUFA up to 1 gram per day. It is also reassuring that no study has reported a significant increase in total mortality associated with dietary of supplemental n-3 PUFA intake.

However, it should also be acknowledged that the antiarrhythmic effects of these agents have not been definitely proven either, and the possibility of proarrhythmia raised by the present study, as well as other potential unforeseen risks associated with n-3 PUFAs, need to be considered further in randomized trials. The data described above illustrates how daunting the task of proving or disproving antiarrhythmic effects of these agents will be in the modern era. Conclusive data will only come from adequately powered randomized trials with SCD and total mortality endpoints; which will require larger study populations or improved risk stratification measures to identify a population at proportionally higher risk for SCD as opposed to other causes of death. In addition, determination of SCD and arrhythmic death is difficult in clinical trials and subject to misclassification, which can be minimized but not eliminated by rigorous adjudication methods. Therefore, effects on total mortality will be more reliable. But to have a significant impact on total mortality, a sufficiently large proportion of the deaths will need to be sudden or n-3 PUFAs will need to have pleotropic effects that also impact other causes of death. Finally, the electrophysiologic actions of n-3 PUFAs may depend not only on the dose, but also on the substrate and mechanism underlying SCD. Therefore, results from trials performed in one patient population may not be able to be extrapolated to another.

Although such randomized trials will be large and expensive to conduct, it is only through such trials that definitive data on the efficacy and risks of n-3 PUFAs will be obtained. It would be unfortunate both to miss the opportunity to prevent SCD with this relatively low-cost intervention or to widely disseminate an intervention which may pose unknown risks to certain sub-groups of patients. If n-3 PUFAs were definitively proven to protect against SCD in the setting of ischemia, the public health impact in terms of quantity and quality of life saved has the potential to be quite large. Therefore, the benefits and risks of omega-3 fatty acids still both requires and deserves to be adequately tested in randomized trials.

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