WORKSHOP EXECUTIVE SUMMARY
Omega-3 Fatty Acids and their Role in Cardiac Arrhythmogenesis: Research Challenges and Opportunities

Date: August 29-30, 2005

Location: Washington, District of Columbia

Purpose: The major goals for this workshop were to: (1) review the epidemiological evidence and the data from NHLBI-supported randomized trials on the role of omega-3 fatty acids in susceptibility to arrhythmias and sudden cardiac death (SCD); (2) explore the basic mechanisms by which omega-3 fatty acids affect cardiac excitability at the cellular and organ level; (3) identify the gaps and barriers in our basic understanding of the effects of omega-3 fatty acids on cardiac electrical activity at the cellular, tissue, and whole body levels; and (4) provide prioritized recommendations for additional research studies to (a) better understand the basic mechanisms coupling omega-3 fatty acids to cardiac electrical activity and (b) facilitate translation of this knowledge to the treatment and prevention of cardiac arrhythmias.

Discussion: Workshop members reviewed the present state of knowledge related to n-3 fatty acids and cardiac arrhythmia mechanisms. Dietary sources and quantification of n-3 fatty acids, competition between n-3 and n-6 fatty acids, pathways for production of tissue n-3 and n-6 highly unsaturated fatty acids, and the importance of adequate measurements in clinical trials were reviewed. Evidence was presented that the risk of either cardiac arrest or sudden death is associated with low dietary intake and blood levels of polyunsaturated fatty acids and that a fish diet (DART) (Lancet 1989;2:757-61) or dietary supplementation with polyunsaturated fatty acids (GISSI-Prevenzione) (Lancet 1999; 354: 447-55) decease mortality and/or sudden death following myocardial infarction. The randomized, double blind Antiarrhythmic Effects of n-3 Fatty Acids Study (JAMA. 2005 Jun 15;293:2884-91) was reported by Dr. McAnulty to show no benefit and a trend towards increased arrhythmias in patients with high arrhythmic risk and ICDs, while the Fatty Acid Antiarrhythmic Trial was reported by Dr. Leaf to show a strong trend towards benefit in a similar population. A review of animal models showed fewer ischemia and reperfusion-induced arrhythmias in rats fed EPA or DHA, but highlighted the limited scope of the animal models studied to date. The evidence for several different mechanisms by which n-3 fatty acids may alter arrhythmias was discussed in detail, including potential effects on cardiac sodium channels, calcium channels, the sodium-calcium exchanger, lipid rafts, calcium release from the sarcoplasmic reticulum, kinases including PKA and CaMKII, and myocardial oxygen stress. Potential anti-inflammatory properties of n-3 fatty acids and the relationship of inflammatory changes to both atrial and ventricular arrhythmias were discussed. Current gaps in our knowledge include the absence of proof that n-3 fatty acids decrease arrhythmias in patients at risk for sudden death, uncertainty as to which patients may benefit most from supplementation, limited mechanistic data from animal models, and no definitive understanding as to which basic mechanisms transduce effects on cardiac electrogenesis.

Recommendations: The following recommendations suggest future approaches to expedite elucidation of the mechanisms of action responsible for the effect of omega-3 fatty acids on cardiac electrical activity and arrhythmogenesis.

- The protocols and data from the prior randomized clinical trials and the ongoing GISSI-HF trial (Eur J Heart Fail. 2004;6:635-41) should be reviewed in detail. A comprehensive comparison of the two completed NHLBI-supported randomized

blinded ICD trials is encouraged, as well as with the third, recently completed Study on Omega-3 Fatty acids and ventricular Arrhythmia (SOFA) (Eur J Clin Nutr. 2003;57:1323-30). The availability of stored serum samples from all prior trials should be ascertained; available serum samples could, for example, be used to test for inflammatory biomarkers.

- Supplementation with n-3 fatty acids did not reproducibly reduce arrhythmia frequency in the three recent ICD trials that studied patient populations with recent documented arrhythmic events. Based on the results of DART, GISSI-Prevenzione and SOFA (http://www.eurekalert.org/pub_releases/2005-09/esoc-ssr090505.php), the ischemic post-MI population may obtain the greatest benefit from n-3 fatty acids. A randomized, double blinded clinical trial to directly test the effect of n-3 fatty acids on arrhythmia frequency in the post-MI population should be considered. Serum samples for inflammatory biomarkers and DNA for genetic studies should be obtained in all future studies.

- n-3 fatty acids may change arrhythmia susceptibility through alterations in ion channel expression and function (especially sodium and calcium channels), membrane lipid composition and fluidity, kinase expression and activity, oxidative stress, inflammation, and other yet-to-be-determined mechanisms. These mechanisms should be further characterized in animals fed diets with low, mid-range, and high amounts of polyunsaturated fatty acids. While no one animal species or arrhythmia model is preferred, a paucity of large animal and ischemic models is noted in the literature. Studies should have a mechanistic focus and could incorporate programmed electrical stimulation in-vivo, optical mapping of isolated hearts, cellular electrophysiology, molecular and enzymatic measurements. Tissue levels of highly unsaturated fatty acids should be determined. Exploratory studies including genomic (microarray), proteomic, and lipidomic approaches would be appropriate. Computer models of the cardiac action potential and tissue models of electrical propagation would also be useful in understanding potential mechanisms by which n-3 fatty acids affect cardiac electrogenesis.

- Preliminary studies focusing on other fatty acids such as (but not limited to) alpha-linolenic acid (ALA) and sterodonic acid should be encouraged. Methods to rapidly and efficiently measure fatty acid composition in blood and tissue samples should be explored.

Publication Plans:
A copy of the agenda for and roster of Workshop participant, as well as of the abstracts of and slides used for each formal presentation is posted at the following NIH website: http://ods.od.nih.gov/pubs/NHLBI-ODS_Omega-3-n-Arrhythmias_Workshop.pdf. A summary of the workshop proceedings and recommendations is being prepared for review by and publication in a peer-reviewed, internationally recognized scientific journal.

Participating NIH Institutes and Centers
National Heart, Lung, and Blood Institute; Division of Heart and Vascular Diseases
National Institutes of Health Office of Dietary Supplements

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