Review Article

Antiarrhythmic effects of n-3 polyunsaturated fatty acids

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The n-3 or omega 3 polyunsaturated fatty acids are a promising dietary preventive therapy for cardiovascular disease. The main dietary source of n-3 polyunsaturated fatty acids comes from sea fish. During recent years, the subject of antiarrhythmic role of n-3 polyunsaturated fatty acids has been investigated extensively. A great deal of evidence has shown that the antiarrhythmic effect of n-3 polyunsaturated fatty acids is exerted by altering the electrophysiology of myocytes. This article is intended to review specifically this role of n-3 polyunsaturated fatty acids as demonstrated by both basic and clinical evidence in animal and human studies, including current concepts on the antiarrhythmic mechanism of this class of polyunsaturated fatty acids.

Key Words: n-3 polyunsaturated fatty acid, omega 3 fats, fish oil, arrhythmia, ischemia, electrophysiology

Introduction

Diet has become an important issue in preventive medicine, especially in regard to cardiovascular diseases.[1] Fatty acids are among the most interesting topics investigated in the past few decades.[2,3] It is known that saturated fatty acids are not healthy, particularly for the heart.[4] However, polyunsaturated fatty acids (PUFAs), particularly long-chain n-3 PUFAs have been shown to have healthy benefits.[1,5-7] There is a growing body of evidence demonstrating that one of the beneficial effects of n-3 PUFAs is their antiarrhythmic effect.

PUFAs are divided into two classes: n-6 and n-3 PUFAs. They both are essential fatty acids that cannot be synthesized in human bodies. The parent form of n-6 PUFA is linoleic acid, which is found mostly in vegetable oils. The parent form of n-3 PUFA is alpha-linolenic acid. It is transformed to be eicosapentaenoic acid (C 20:5 n-3, EPA) and docosahexaenoic acid (C 22:6 n-3, DHA) by desaturation and elongation. The main dietary sources of long chain n-3 PUFAs (EPA and DHA) include from sea fish or meat from fish-eating animals, eg. seals, and can also be found in flaxseed, rapeseed (canola), linseed, perilla oil and some nuts in lesser amounts.

Both n-3 and n-6 PUFAs have been shown to have antiarrhythmic effects, whereas monounsaturated oleic acid and the saturated fatty acids such as stearic, palmitic, and lauric did not.[8] However, cyclooxygenase products of arachinoic acid (C 20:4, n-6), which is transformed from its parent form of n-6 PUFAs (linoleic acid), have been shown to cause arrhythmia *in vitro*.[9] This arrhythmogenic effect was not found in cyclooxygenase products of EPA.[9] According to these findings from animal studies, long-chain n-3 PUFAs are the only fatty acid class currently recommended for human clinical trials.[10]

Clinical evidence of the antiarrhythmic role of n-3 PUFAs

The evidence from epidemiologic studies has shown that the populations with a high dietary fish intake, such as Greenland Eskimos,[11] Alaskan natives,[12] and Japanese residing in fishing villages,[13] had a lower rate of cardiovascular diseases, leading to the postulation that fish consumption may protect against cardiovascular diseases. Subsequently, prospective cohort studies[14-18] have demonstrated additional evidence with an inverse association between fish consumption and risk of coronary heart disease. The Physicians' Health Study[19] followed a group of male physicians for 17 years. Blood was collected and analysed for a baseline fatty acid composition in 94 men who later presented with a sudden cardiac death event as their first manifestation of cardiovascular disease. A group of 184 age-matched and smoking-habit matched men served as controls. This study reported that a baseline blood level of long-chain n-3 PUFAs was inversely related to the risk of sudden cardiac death.

The report from the Diet and Reinfarction Trial (DART),[20] a randomised, multifactorial, dietary interventional study, examined more than 2000 Welsh men with recent myocardial infarction. These men were separated into three groups according to dietary interventions: fat intake reduction, increment of fiber intake, and an increase

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in fatty fish intake. After a 2-year follow up, the fatty fish supplement group had a 29% reduction in mortality compared with the other 2 groups, suggesting a beneficial effect of PUFAs on reduction of sudden cardiac death.

In the Lyon Heart study,[21] a prospective, randomised, single-blinded, secondary prevention study was aimed at testing whether a Mediterranean-type diet (n-3 PUFA, oleic acid, antioxidant vitamins) could reduce the rate of recurrence after the first myocardial infarction, compared with a western-type diet. After a 4-year follow up, the Mediterranean diet group was found to contain more n-3 PUFAs in plasma phospholipids and had a 70% reduction in all-cause mortality and morbidity compared to the western type diet group.

The Gissi-Prevenzione study,[22] a randomised, open, parallel-group, was designed to explore the independent and combined effects of n-3 PUFAs and vitamin E in 11,324 patients with recent myocardial infarction during the previous 3 months. After a 3.5-year follow up, the group with n-3 PUFAs treatment, but not the group treated with vitamin E, had a significant reduction in the composite endpoint of death, nonfatal MI, or nonfatal stroke (10% on 2-way analysis, 15% on 4-way analysis; $P = 0.048$ and $P = 0.023$, respectively) and of cardiovascular death, non-fatal MI, or nonfatal stroke (20% on 4-way analysis; $P = 0.008$).

The results from the DART and Gissi-Prevenzione studies have elucidated the role of n-3 PUFAs in the reduction in mortality, but not myocardial infarction, suggesting that the beneficial effect of this class of fatty acids was attributable to a reduction in arrhythmic death.[23] Furthermore, the DART, the Lyon Heart study and the reanalysis of Gissi-Prevenzione studies[24;25] have demonstrated that the very early divergence of survival curves occurred only in the first few weeks or months of the trials, earlier than the secondary prevention study of statin trials[26-28] in which the divergence of survival curves occurred after 2 years.

A recent pilot study of Schrepf and colleagues[29] was designed to assess the direct antiarrhythmic effect of n-3 PUFAs in the high risk group of sudden cardiac death patients. They conducted the study in 10 patients who had implanted cardioverter defibrillators with repeated episodes of documented, sustained ventricular tachycardia. Electrophysiological studies were done before and immediately after the infusion of 3.8g n-3 PUFAs. Their finding demonstrated that the infusion of n-3 PUFAs resulted in a reduction of sustained ventricular tachycardia in 5 of 7 patients and did not induce arrhythmia. All or these clinical and epidemiologic studies have strongly confirmed the antiarrhythmic effects of n-3 PUFAs.

Prevention of ischemia-induced arrhythmia by n-3 PUFAs

A number of studies on n-3 PUFAs have demonstrated that it can prevent ischemia-induced fatal ventricular arrhythmia in animals, and probably in human.[30-34] McLennan and colleagues[33,34] reported that ischemia-induced ventricular arrhythmia, generated by ligation of coronary arteries, were prevented in the tuna fish oil-fed rats, while saturated fatty acid-fed rats suffered 43% mortality from ventricular fibrillation. Billman and colleagues[30-32], using a dog model of sudden cardiac death, have demonstrated similar findings. In their study in dogs, a large myocardial infarction on the anterior wall was produced by surgical ligation of the left anterior descending artery. An inflatable cuff was placed around the left circumflex coronary artery for inducing myocardial ischemia. They were trained to run on a treadmill 1month after the surgery. During running on the tread-mill, the left circumflex artery was occluded and regularly caused ventricular fibrillation in all dogs. One week later, the test was performed again after administration of n-3 PUFAs intravenously. With infusion of the eicosapentaenoic acid, 5 of 7 dogs were protected from fatal ventricular arrhythmia ($P<0.002$). With docosahexaenoic acid, 6 of 8 dogs were protected, and with alpha-linolenic acid, 6 of 8 dogs were also protected ($P<0.004$ for each). After one week, this exercise-plus-ischemia test was repeated without n-3 PUFAs administration in the same animals, and resulted in fatal ventricular arrhythmias in all dogs.

Mechanism of antiarrhythmic action of n-3 PUFAs

A great deal of evidence has shown that the antiarrhythmic effect of n-3 PUFAs acts by altering the electrophysiology of myocytes.[23,35,36] This occurs via at least two mechanisms: modulation of ion channels[37-40] and inhibition of the calcium release mechanism of sarcoplasmic reticulum.[41]

The n-3 PUFAs main antiarrhythmic effect occurs by blocking the voltage-gated sodium channel.[40,42] The inhibitory effect of n-3 PUFAs exerts mainly in an inactive state, producing a large voltage-dependent shift (10-20 mV) in the potential for one half steady state inactivation (V1/2) to a more hyperpolarized value.[40] This leads to stabilizing the inactivated state of the channel and accelerating the transition from the resting to the inactivated state.[43,44] Furthermore, blocking voltage-gated sodium channel by n-3 PUFAs causes slight, but significant, hyperpolarization of the resting membrane potential of the myocyte, and increases the voltage threshold for gating the fast sodium channel.[35] These result in a 50% increase in the strength of an electrical stimulus to elicit an action potential and a marked prolongation of the relative refractory period (phase 4 of cardiac cycle) of the myocytes in the presence of the n-3 PUFAs.[35] These effects will enhance the electrical stability of the heart to lethal arrhythmias.[44]

During myocardial ischemia, myocardial cells at a central core will be quickly depolarized due to a dysfunctional state of sodium-potassium ATPase and die from lack of oxygen and metabolic substrates.[45] However, myocardial cells at the periphery of the ischemic zone will be only partially depolarized, leading to an hyper-excitable state of these cells since the resting membrane potential is positively shifted close to the threshold of the fast-gated sodium channel.[44] As a result, a small depolarizing stimulus can produce an action potential. In addition, if the action potential arises at the vulnerable period, it can initiate aberrant conduction and resultant arrhythmias.[10] The voltage-gated sodium channel blocking

effect of n-3 PUFAs can be beneficial in preventing arrhythmias in this situation.

The n-3 PUFAs have been shown to inhibit the L-type voltage-gated calcium channel.[39] It is known that the L-type calcium channel plays an important role in the exciting-coupling mechanism of cardiomyocyte contraction.[46] The n-3 PUFAs inhibit calcium influx into the cell through the L-type calcium channel and also inhibit the calcium induced-calcium release mechanism.[39] The n-3 PUFAs also causes a negative shift of steady state inactivate curve of calcium current.[39] Furthermore, recent *in vitro* studies[41,47,48] have demonstrated that n-3 PUFAs have an inhibitory effect on sarcoplasmic reticulum calcium release mechanism by directly inhibiting the calcium release channel (ryanodine receptor) via more than one mechanism.[41] The postulated mechanisms include the part of activating intracellular enzyme pathway, indirectly modifying gating of ryanodine receptor, or reduction of channel opening probability by interacting more locally with ryanodine channel complex.[41]

In ischemic myocardial cells, calcium overload can be developed under the influence of β-adrenergic agonists, Na^+-Ca^{2+} exchange mechanism, and an impaired calcium uptake by the sarcoplasmic reticulum.[8,36] Delayed after depolarization has been shown to be induced more readily in this situation.[45] The n-3 PUFAs are of benefit in this situation since their inhibitory effect of L-type calcium channel and calcium release channel (ryanodine receptor) impedes an overload of the intracellular calcium.[39]

Besides the inhibitory effect of n-3 PUFAs on voltage-gated sodium and calcium channels, n-3 PUFAs also inhibit transient outward current (I_{TO}) and delayed rectifier (I_K) current, but not inward rectifier (I_{K1}) current, and also some ligand-gated channels such as cAMP-dependent chloride channel, acetylcholine dependent potassium channel.[37,49] Although the reduction in potassium efflux usually produces prolongation of action potential duration, this does not occur from the effect of n-3 PUFAs.[23]

It has been shown that when myocardial cells develop ischemia, fatty acids will be released from cardiac cell membrane by phospholipase A2.[50,51] If there is a great amount of n-3 PUFAs in cell membrane components, it will release more n-3 PUFAs during ischemia and will increase their effectiveness in protecting against arrhythmia.[32,34]

Theoretical adverse effects of n-3 PUFAs

Recent guidelines recommend that the general public should regularly consume fish as part of a healthy diet.[1,6] The n-3 PUFAs have been listed on the GRAS (generally regarded as safe) list according to the Food and Drug Administration in amounts up to 3.5g of fish oil per day.[1,6] Nevertheless, there are some concerns regarding the adverse effects of n-3 PUFAs. According to CAST I study,[52] class I antiarrhythmic drugs, i.e. Na^+ channel inhibitors, the same as n-3 PUFAs, are not safe since they cause higher mortality in coronary artery disease patients than the placebo. Kang and colleagues[53] studied the effect of n-3 PUFAs and mexiletin on mRNA expression and the number of Na^+ channels per cell of neonatal rat myocytes. They reported that mexiletin increased five times the number of Na^+channels and caused an over-expression of mRNA encoding alpha-subunit of Na^+ channel protein. However, n-3 PUFAs did not increase the number of Na^+channels and did not upregulate mRNA encoding for Na^+channel protein. It is possible that their different effects might be at the level of the gene. Therefore, if n-3 PUFAs really have some adverse effects, it will not be associated with the over-expression of Na^+ channel and mRNA encoding for Na^+channel protein.[10]

There is another hypothetical mechanism of n-3 PUFAs' adverse effect. The n-3 PUFAs action prevails on partially depolarized cells at the periphery of the ischemic zone after myocardial infarction, causing prompt and complete inactivation of these cells by modulation of ion channels, and inhibiting calcium release by the sarcoplasmic reticulum. This effect will abort the potential arrhythmic role of the partially depolarized ischemic cells. However, this effect does not involve normal myocytes. Therefore, there are still sufficient normal myocardial cells to sustain the pumping action of the heart, even when partially depolarized myocyte function has been eliminated by n-3 PUFAs. But in the case of diffuse myocardial ischemia, there are plenty of partially depolarized myocytes populating the myocardium. If all ischemic cell function is eliminated by n-3 PUFAs, it will cause insufficient contractile force and the heart will fail as a pump. Consequently, patients will possibly die from asystole. The malignant arrhythmia can also occur because in diffuse ischemic myocardial environment, some partially depolarized ischemic myocytes are likely to elicit aberrant Na^+ current and initiate arrhythmia.[10] This effect resembles the bidirectional effect of diltiazem, which is beneficial in a majority of patients with well-preserved left ventricular function but harmful in a minority of patients with impaired ventricular function.[54]

Debates on in the antiarrhythmic effect of n-3 PUFAs in humans

Although a number of reports have demonstrated the beneficial effect of n-3 PUFAs, there is still some debate, particularly on the antiarrhythmic effect of n-3 PUFAs in humans.[10] A recent clinical trial investigated the antiarrhythmic effect of n-3 PUFAs in 200 patients either with a recently implanted internal cardiac defibrillator (ICD) for an episode of sustain ventricular tachycardia or ventricular fibrillation, or with an ICD that had discharged appropriately within the previous 3 months.[55] The patients who had received antiarrhythmic drugs class I or III were excluded from the study. The enrolled patients were divided into two groups, one received 1.8 gram of fish oil and the other received olive oil. After a 2-year follow up, there was a non-significant trend toward an increased risk of ventricular arrhythmia in the fish oil group. Subgroup analysis suggested that patients in the fish oil group who had received an ICD for sustained ventricular tachycardia had significantly more arrhythmias, while patients who had received an ICD for ventricular fibrillation tended to have a reduction in arrhythmic events. There were fewer deaths overall in the fish oil group, but this was not significant. This trial suggested that if n-3 PUFAs do reduce mortality, they might do so by a mechanism other than reduction in ventricular arrhythmias. However, since the substrate for the induction of

ventricular tachycardia and ventricular fibrillation may be different, a specific effect on ventricular fibrillation suppression cannot be excluded. The limitation of this trial is the lack of placebo-control group. Also, despite the fact that olive oil has no direct anti-arrhythmic effect, it can compete with n-6 PUFAs in the diet or within cell membranes. This will shift the n-6/n-3 PUFAs ratio from $\geq$ 15:1 (which has been estimated for current American diet) to the "ideal" 1:1.[56] This effect caused by olive oil may favor the effects of n-3 PUFAs from their usual diet and therefore, may dilute the beneficial effect of n-3 PUFAs in this trial.

Conclusion

The n-3 PUFAs have an established antiarrhythmic effect as demonstrated in animal, epidemiologic, as well as clinical studies. However, it is still unclear whether the anti-arrhythmic actions of n-3 PUFAs actually prevent fatal arrhythmias. The two secondary prevention trials; DART and Gissi-prevenzione study have elucidated the reduction in mortality, but not myocardial infarction. This suggests that the beneficial effect of n-3 PUFAs was attributable to a reduction in arrhythmic death.[7] The recent clinical trial in patients with implanted ICDs also found no reduction in ventricular arrhythmias in the fish oil group.[55] Large, prospective randomized placebo-controlled clinical studies on antiarrhythmic effects of n-3 PUFAs are needed to verify the antiarrhythmic role of this class of fatty acids in various clinical settings.

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Antiarrhythmic effects of n-3 polyunsaturated fatty acids
n-3 多不饱和脂肪酸抗心律失常作用

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n-3 或ω3 多不饱和脂肪酸是一种对心血管疾病大有前途的膳食预防性治疗剂。海洋鱼类是 n-3 多不饱和脂肪酸的主要膳食来源。近些年来，人们对多不饱和脂肪酸的抗心率失常作用进行了广泛的研究。大量证据已经表明 n-3 多不饱和脂肪酸抗心率失常作用是通过改变肌细胞电生理学而达到的。本文旨在对 n-3 多不饱和脂肪酸的抗心率失常作用及其作用机制作一综述，n-3 多不饱和脂肪酸这种抗心率失常作用是由动物和人体实验所获得的基础和临床证据而得到证实的。

关键词：n-3 多不饱和脂肪酸， ω3 脂肪，鱼油，心率失常，局部缺血，电生理学