Impact of Dietary Fatty Acids on Cardiac Arrhythmogenesis

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A recent headline on theHeart.org was “Western Diet Increases MI Risk Worldwide.” In the past 30 years, it has become apparent that dietary fatty acids have a profound impact on the composition of plasma and cardiovascular tissue lipid pools, and as a result, on the risks of cardiovascular disease. Although significant progress has been made to reduce the incidence of death caused by coronary heart disease, it still afflicts ∼450,000 patients per year in the United States, with many of these dying from cardiac arrhythmias.1 Atrial fibrillation (AF), the most common arrhythmia, affects more than 2.2 million Americans. It has been estimated that more than 12 million Americans will have AF by 2050 because of the aging of the population as well as the increasing incidence of diabetes and obesity, both risk factors for AF.1 Reasons underlying the increased prevalence of these acquired diseases are complex, involving societal changes in diet, lifestyle, and physical activity. Efforts to address these risk factors seem likely to reduce the burden of cardiac arrhythmia and cardiovascular disease. Although all are important, this review focuses on the relationship between dietary fatty acids and mechanisms of cardiac arrhythmogenesis.

**Dietary Fatty Acids**

**What Fatty Acids Are Present in the Diet?**

As shown in Figure 1, fatty acids consist of a straight chain of carbon atoms with a carboxylic end (COOH) and a methyl (CH₃) or omega end and are classified based on the saturation of the carbon chain. Common saturated fatty acids, those with no double bonds, include palmitic acid (16:0) and stearic acid (18:0). Foods high in saturated fatty acids include dairy products, red meats, and tropical oils.2 Unsaturated fatty acids are further classified based on the number and location of double bonds. Monounsaturated fatty acids, such as oleic acid (18:1n9), have a single double bond, whereas polyunsaturated fatty acids (PUFA) have multiple double bonds. ω6 PUFA, such as linoleic acid (LA, 18:2n6) and arachidonic acid (AA, 20:4n6), have the first double bond located at the sixth carbon (when counting from the omega end) and are found readily in dietary sources such as vegetable oils, meat, eggs, and dairy. ω3 PUFA, such as α-linolenic acid (ALA, 18:3n3), eicosapentaenoic acid (EPA, 20:5n3), and docosahexaenoic acid (DHA, 22:6n3), have the first double bond located at the third carbon. Although ALA is found in flax seed and other plants, EPA and DHA are primarily found in fatty fish, such as salmon.2

**How Are Dietary Fatty Acids Used and Stored by the Body?**

Dietary fatty acids are metabolized as fuel for oxidative phosphorylation, stored as triglycerides, or rapidly incorporated into plasma phospholipids, high-density lipoprotein particles, and cell membranes. Fatty acids seldom exist in a “free” form; nonesterified fatty acids are bound by plasma albumin. The mass of lipids incorporated into the various lipid pools limits the kinetics of turnover. Plasma triglyceride composition can be modified within days of a dietary modification, but changes in cardiac tissue lipid composition resulting from dietary changes require several weeks to reach steady state. In patients scheduled for cardiac surgery (with low dietary fish intake), a 1-month treatment with fish oil (2.9% energy as EPA and DHA, 3 g/d) raised the content of those lipids in the right atrial appendage (removed at surgery) from 5.3% to 11.5%, and decreased the AA content from 21% to 16%.3 Interestingly, dietary supplementation with energy equivalent quantities of ALA or olive oil had no significant impact on cardiac lipid composition.3 Experimental studies also show that diets enriched with long-chain ω3 PUFA lead to ω3 PUFA incorporation into cardiac tissues.4,5

**Epidemiological Data Show That Dietary Fatty Acids Affect Cardiovascular Health**

Epidemiological studies suggest that the composition of dietary fatty acids (eg, saturated versus unsaturated; ω3 versus ω6, etc) has important consequences for cardiovascular health and cardiac arrhythmogenesis.6 Saturated and trans-fats increase cardiovascular risk.6 Both ω3 and ω6 PUFA have shown some evidence of cardiovascular benefit.7,8 Regional and ethnic differences in food availability and preference result in significant variations in dietary fatty acid composition. Hibbeln et al8 reported an inverse relationship between dietary ω3 PUFA intake and mortality resulting from cardiovascular disease, with the lowest mortality reported in countries such as Japan, Greenland, and Iceland, whose citizens have the highest proportion dietary lipid calories derived from ω3 PUFA. Interestingly, the proportion of dietary calories derived from fat was high in Greenland and relatively low in Japan, yet both countries showed decreased...
cardiovascular risk. Although dietary ALA is more readily available (from plant-based sources), evidence is stronger for a cardiovascular benefit of EPA and DHA than for ALA.9 Among the ω6 PUFA, a recent AHA advisory cites several epidemiological and prospective cohort studies showing that individuals with the highest tissue/blood levels of LA had the lowest cardiovascular risk.7

AHA Guidelines for Dietary Fats
The American Heart Association (AHA) recognizes that dietary fatty acids and cardiovascular disease risk are interrelated. Current AHA Dietary Guidelines recommend limiting total fat intake to <35% of daily calories, with saturated fat <7% of daily calories, and the remainder coming from monounsaturated and polyunsaturated fats.2 It is intriguing, however, that the Women’s Health Initiative reported that a low-fat diet did not significantly affect cardiovascular disease incidence and only modestly altered the risk factors for cardiovascular disease.10

Stress-Dependent Effects of Dietary Fats
The impact of dietary fatty acids on cardiovascular function under normal conditions may differ from that under conditions of hemodynamic, ischemic, or autonomic stress. Under normal conditions, fatty acids are used for many cellular processes; however, when lipid availability exceeds the capacity for utilization, fatty acids can alter mitochondrial structure11 and function, increasing lipid peroxidation,12 mitochondrial uncoupling, and reactive oxygen species production,13 eventually leading to cytochrome c release, caspase activation, DNA laddering, and apoptosis.14,15 Despite evidence showing that dietary fat can be cytotoxic, dietary fat appears cardioprotective in several animal models of left ventricular dysfunction. Studies in the Dahl salt-sensitive rat model of hypertension-induced cardiomyopathy,16 a mouse model of transverse aortic constriction,17 and a rat model of abdominal aortic banding18 have shown that 60% high saturated fat feeding did not exacerbate the hypertrophic response to injury. A 60% high saturated fat diet in a rat model of coronary artery ligation–induced heart failure also did not adversely affect myocardial contractile function but increased mitochondrial enzyme activities and oxidative phosphorylation.19,20 These alterations in mitochondrial function were not evident in sham animals fed high saturated fat,19 suggesting that the effects of a high fat diet represented responses to pathological stress. In a subsequent study, mitochondrial oxidative phosphorylation was unaltered in rats fed a high fat diet after ligation surgery but was decreased in sham animals fed the high fat diet.21 However, the proarrhythmic consequences of such a diet are notable; rats fed the same high fat diet before coronary artery ligation had an increased risk of sudden death early after myocardial infarction.20 These studies suggest that manipulation of dietary fat content and composition can have different effects under normal versus pathological conditions and that ischemic and hemodynamic stressors can modify the outcome.

Arrhythmogenic Mechanisms Affected by Dietary Fatty Acids
Dietary fatty acids can promote and/or prevent cardiac arrhythmia via several pathways (Figure 2), including (1) modulation of electrophysiological and metabolic heterogeneities secondary to atherosclerotic disease, (2) modulation of cardiac myocyte metabolic activity and cardiovascular oxidant stress, (3) direct modulation of ion channel and transporter activity, (4) indirect modulation of ion channel and transporter activity, via modulation of autonomic nervous system activity, and (5) modulation of inflammatory pathways that promote ectopic electric activity and abnormal conduction. These mechanisms are considered in the paragraphs below.

1: Dietary Fatty Acids, Atherosclerosis, and Arrhythmogenesis
Elevated blood cholesterol and triglycerides are associated with increased risk for cardiovascular disease.1 Although
dietary saturated fat increases cardiovascular risk,6 ω3 PUFA have been shown to decrease plasma triglyceride content16,22,23 and cardiovascular risk. One potential antiarrhythmic mechanism involves modulation of the extent of atherosclerosis and subsequent cardiac ischemia.

The impact of dietary fatty acid composition on the development of atherosclerosis was recently evaluated in 3 different populations: Japanese men living in Japan, American men, and men of Japanese origin living in the United States.24 The Japanese men living in Japan consumed a diet more enriched in ω3 PUFA than the American diet and had less atherosclerosis, with a significant inverse relationship between serum ω3 PUFA levels and carotid intima-media thickness.25 Japanese men living in the United States had more atherosclerosis than either the native Japanese or American men, suggesting that genetic factors do not underlie this relationship.24 This and other studies suggest that consumption of a diet enriched in ω3 PUFA is antiatherogenic. The GISSI Prevenzione trial reported that consumption of a Mediterranean diet supplemented with 1 g per day of ω3 PUFA (but not vitamin E) was associated with a 45% reduction in the incidence of sudden cardiac death.28 Animal studies also have shown that dietary manipulation of lipid composition profoundly affects cardiac arrhythmogenesis. Pepe et al26 reported that animals fed a diet enriched with saturated fat had increased susceptibility to ventricular fibrillation and tachycardia after ischemia and reperfusion; fish oil supplementation reversed these effects. Although atherosclerosis-induced ischemia is an important element of arrhythmogenesis, it is not the only factor affected by dietary fatty acids.

2: Impact of Dietary Lipids on Cardiac Metabolism and Arrhythmogenesis

Arrhythmias frequently occur in the metabolically challenged heart, consistent with the hypothesis that metabolic instability underlies electric instability.27 Possible mediators include insufficient ATP for contractile and ion cycling requirements, lack of oxygen, lack of substrate availability, or impaired enzymatic activity.27 Fatty acids are the primary energy substrate in the healthy heart. With the development and progression of ventricular dysfunction, expression of the primary transcriptional regulator of fatty acid metabolism in the heart, peroxisome proliferator activated receptor-α (PPARα), and enzymes involved in fatty acid oxidation are downregulated.28–30

Studies in human31 and animal heart failure models have reported abnormalities in mitochondrial morphology,32 damage to the phosphorylation apparatus, and decreased mitochondrial respiration33–35 and electron transport chain activities.36,37 Atrial tissues from patients with AF show evidence of abnormal mitochondrial morphology,38 deletion of mitochondrial DNA segments,39 decreased oxidative phosphorylation,38 and increased proton leak.40 Changes in atrial mitochondrial structure similar to those that occur in heart failure seem likely to contribute to the progression of AF; however, alterations in atrial energetics during the progression of AF are currently less well characterized than in the failing ventricle.

Although the role of metabolic alterations in arrhythmogenesis is not well understood, there is a clear association between dietary lipids and metabolism. Specific actions of fatty acids can vary, depending on the composition of the fatty acid (saturation, chain length, etc). For example, fatty acids are natural ligands for PPARα, but long-chain unsaturated fatty acids are more effective ligands than long-chain saturated and short-chain fatty acids.41,42 Dietary PUFAs lower plasma16,22,23 and tissue triglycerides43; however, dietary ω3 PUFAs (EPA, DHA, and ALA) decrease serum triglycerides and phospholipids more effectively than LA (an ω6 PUFA).43 Supplementation of an ALA-enriched diet with EPA/DHA has been reported to further increase the expression of genes involved in mitochondrial biogenesis and fatty acid oxidation.44 It seems plausible that diets enriched in protective fatty acids (eg, LA, ALA, EPA, and DHA) could decrease metabolic stress and reduce the incidence of metabolically induced arrhythmias.

Oxidant Stress in Heart Failure and Arrhythmia

Failing hearts frequently show signs of oxidative stress,45,46 including lipid peroxidation, protein nitration, and other post-translational modifications induced by the interaction of reactive oxygen and nitrogen species with cellular proteins and lipids. Our group was the first to show evidence of oxidative stress in the atria of patients with AF,47 with increased nitrotyrosine abundance (a marker of peroxynitrite formation) in atria from AF patients. Others have shown that the redox state is more oxidized and that markers of oxidant stress are elevated in the plasma of patients with AF.48

Mitochondria are a major source of oxidative generation and an important target for oxidative damage. Cardiolipin, a phospholipid unique to the mitochondrial inner membrane, is susceptible to oxidative modification because of its highly unsaturated structure and its proximity to the electron transport chain.39 Because cardiolipin plays an essential role in the structure and activity of electron transport chain complexes, alterations in cardiolipin content have serious implications for mitochondrial energy production. The resulting inhibition of the electron transport chain can promote generation of reactive oxygen species at complexes I36 and III.37 Oxidant
production also can result in modification of mitochondrial proteins. Reactive nitrogen species inhibit the activity of mitochondrial enzymes aconitate, catalase, and glutathione peroxidase, as well as various components of the electron transport chain.50

Oxidant stress is increased in patients after cardiac surgery. In a small, case-controlled study, serum total peroxide levels and right atrial protein oxidation at 6 hours after cardiac surgery were greater in patients who later had postoperative AF than in those who did not.51 A proteomic analysis of atrial tissues from surgical patients reported that patients who had postoperative AF also showed evidence of metabolic alterations and depletion of the antioxidant protein peroxiredoxin.52 Preservation of cardiac mitochondrial function, therefore, could be an important step toward preventing disease progression.

Mitochondrial oxidant generation is sensitive to dietary lipid composition. Experimentally, a cholesterol-rich diet promoted increased superoxide production, nitrotyrosine abundance, and cardiac dysfunction;53 however, expression of cardiac antioxidants Mn-superoxide dismutase and glutathione peroxidase was enhanced in rats fed an ω3 PUFA-enriched (EPA and DHA) diet compared with those fed a saturated fat diet.54 Additionally, ω3 PUFA supplementation of a diet rich in saturated fats increased the efficiency of oxygen utilization and inhibited arrhythmias associated with ischemia and reperfusion.55 Together, these studies provide evidence that dietary ω3 PUFA enrichment may attenuate arrhythmia risk, in part by preserving mitochondrial function.

3: Modulation of Ion Channel and Transporter Activity

Intracellular sodium and calcium homeostasis is a critical determinant of arrhythmogenesis, and levels of these ions are coregulated by the activity of the sodium-calcium exchanger (NCX). NCX normally provides a brief period of calcium extrusion during the action potential plateau. Increased intracellular sodium levels resulting from rapid heart rate or altered sodium channel inactivation impede NCX-mediated calcium extrusion during the action potential plateau. Increased intracellular sodium levels resulting from rapid heart rate or altered sodium channel inactivation impede NCX-mediated calcium extrusion. Although elevated cytosolic calcium can have a positive inotropic effect, calcium overload has metabolic, arrhythmogenic, and contractile consequences. In patients with AF, atrial NCX protein expression was increased by 67% relative to control patients with no history of AF.59 NCX current is sensitive to the lipid composition of the membrane and to plasma lipids. In porcine ventricular myocytes, dietary fish oil supplementation prevented calcium overload and reduced the incidence of triggered activity in response to norepinephrine exposure.60 Fatty acid block of NCX is isoform specific; whereas NCX1.1 is only blocked by ω3 PUFAs (EPA, DHA), multiple fatty acids can inhibit NCX1.3 currents.61 Modulation of calcium influx is an important element underlying the beneficial effects of ω3 PUFAs on cardiac electric activity.

Exposure of myocytes to oxidant stress is reported to increase reverse-mode NCX activity and protein expression, to delay the inactivation of the sodium current, and to modulate NCX current, in part secondary to the increased sodium load resulting from oxidant modified sodium channels.62 Delayed sodium channel inactivation, often referred to as “late” sodium current, has been documented in myocytes from failing hearts63 and in human atrial myocytes.64 Sodium entry via late sodium current can prolong the action potential plateau, resulting in increased intracellular sodium load, increasing risk of early afterdepolarizations and triggered and ectopic electric activity.65 Fish oil–derived ω3 PUFAs (EPA and DHA) suppress late sodium current in cells expressing recombinant human cardiac sodium channels.66

In the setting of ischemia, lipid metabolism is a critical modulator of cardiac electric activity. Under ischemic conditions, phospholipase A2 is activated, promoting the release of fatty acids such as AA (ω6 PUFA) and lysophospholipids from the cell membrane. In regional ischemia, AA and lysophospholipid release contribute to the development of proarhythmic heterogeneities of conduction velocity and repolarization. AA can uncouple gap junctions, leading to conduction slowing, and modify the activity of voltage-dependent sodium, calcium, and potassium channels. AA metabolites can modify cardiac ion channel activity (isoketals) and activate G-protein–coupled receptors (EP, FP) that promote ectopic electric activity. Lysophospholipids also modulate ion channel and mitochondrial activity.67,68

The quantity of AA released during ischemia is dependent on its abundance in the cell membrane, which is sensitive to dietary fatty acid composition. In a canine acute infarction model, pretreatment with a diet enriched with ω3 PUFA attenuated the arrhythmogenic response to ischemia.69 Similarly, patients who had ventricular fibrillation during a first myocardial infarction were reported to have lower levels of ω3 incorporated into cell membranes than those who did not.70 Thus, the type of dietary fatty acids incorporated into cardiac membranes is an important determinant of the electrophysiological response of the heart to ischemia.

Antiarhythmic Effects of Infusion/Superfusion Versus Dietary Incorporation of Fatty Acids

To probe the therapeutic benefit of modifying lipid composition on cardiac electric activity, several studies have evaluated the effects of acute infusion of lipid emulsions on experimentally induced arrhythmias. In a canine model of ischemia during exercise after myocardial infarction, Billman et al71 showed that infusion of either ω3 PUFA-enriched emulsion protected animals from sudden death caused by lethal ventricular fibrillation. Emulsions containing individual ω3 PUFAs (EPA, DHA, or ALA) were similarly protective.72 Antiarrhythmic efficacy was associated with a slower heart rate, shorter Q-T interval (corresponding to effects on ventricular action potential duration), reduced left ventricular systolic pressure, and prolonged atrial-ventricular conduction time (P-R interval of the ECG).73 In normal dogs given an acute infusion of either ω3 PUFA or ω6 PUFA, neither PUFA affected atrial effective refractory period (aERP), R-R interval, P-wave duration, P-Q interval, QRS duration, QT or QTc interval over a 6-hour period.74 However, after 6 hours of rapid atrial pacing, infusion with the ω3 PUFA but not the ω6 PUFA attenuated the characteristic pacing-induced abbreviation of aERP.75,76
Lipid infusion/superfusion may not accurately predict the cellular response to dietary fatty acids. In cultured neonatal cardiac myocytes, acute superfusion with DHA (ω3) but not AA (ω6) also slowed spontaneous beating rate, decreased calcium influx via L-type calcium channels, and attenuated the response of the calcium channel to the dihydropyridine agonist Bay K 8644. Dietary changes in ω3 PUFA consumption have a more subtle electrophysiological impact than the acute effects of lipid infusion or superfusion. Whereas superfusion of isolated myocytes with ω3 PUFAs (EPA) acutely suppressed sodium current,80 electrophysiological studies of ventricular myocytes isolated from pigs administered an ω3 PUFA–enriched diet for 8 weeks showed no evidence of altered sodium current density or voltage-dependent channel activation.81 Nonetheless, dietary administration of ω3 PUFA is associated with alterations in ion channel/exchanger activity. Consistent with the acute superfusion studies, a hyperpolarizing shift in sodium channel steady-state inactivation was observed in pigs fed an ω3 PUFA–enriched diet.81 Ventricular myocytes from these animals had attenuated NCX currents, an abbreviated action potential duration, and an ≈20% reduction in peak L-type calcium current density, with no change in voltage-dependent activation or inactivation parameters.81 Diastolic calcium levels and calcium transient amplitude were not altered in animals receiving the ω3 PUFA–enriched diet, but decay of the calcium transient was accelerated.81 Inward rectifier K+ current (IK1) and slow delayed rectifier K+ current (IKs) densities were increased.81 Overall, this study suggests that dietary ω3 PUFA supplementation shortens ventricular action potential duration, simultaneously decreasing the occurrence of early afterdepolarizations and triggered arrhythmic activity via altered action potential duration and changes in cytosolic calcium handling.

4: Autonomic Modulation of Ion Channel and Transporter Activity

Heart rate is controlled by parasympathetic (vagal) and sympathetic (β-adrenergic) nerves innervating the sinoatrial and atrioventricular nodes. Excessive stimulation of either parasympathetic or sympathetic nerves promotes arrhythmogenic responses,82 due either to atrial action potential shortening (strong vagal stimulation) or excessive calcium influx (calcium channel phosphorylation due to adrenergic phosphorylation). In the (small) subset of young, athletic individuals with AF, increased vagal tone and slow heart rate may contribute to the onset of AF.

In the majority of individuals with senile AF, the patients have elements of the metabolic syndrome (obesity, dyslipidemia, insulin resistance, hypertension). Vagal withdrawal occurs in patients with metabolic syndrome and heart failure, leading to sympathetic dominance, abnormal heart rate variability,93,84 and elevated resting heart rate85 (Figure 2). Although sympathetic stimulation can provide for acute increases in calcium influx, contractility, and energy production, persistent sympathetic activation promotes ectopic electric activity and initiation of the apoptotic cascade.86 Interventions that improve vagal tone, including exercise and dietary ω3 PUFA supplementation, favorably affect mechanisms of cardiac arrhythmogenesis, potentially due to vagal modulation of heart rate and calcium cycling.87 Vagal activity also has anti-inflammatory effects, protecting the heart from the deleterious effects of excessive cytokine stimulation.88

Several clinical studies have reported decreased heart rate after increased dietary fish intake89 and administration of fish oil capsules.89–92 A modest improvement in heart rate variability was reported in individuals with high fish consumption,93 consistent with improved vagal tone. However, in a small study of patients after myocardial infarction, 1g/d ω3 PUFAs did not affect heart rate variability.94 Similarly, a study by Geelen et al95 reported no change in heart rate variability or baroreceptor sensitivity in healthy subjects after fish oil supplementation. Factors influencing the response of heart rate and heart rate variability to dietary ω3 PUFAs may include (1) the baseline plasma and tissue lipid composition, (2) the baseline systemic inflammatory and autonomic state, (3) the dose and duration of ω3 PUFA supplementation, and (4) the specific composition of ω3 PUFAs in the diet (as ALA, EPA, and DHA have distinct effects).5,96,97

5: Modulation of Inflammatory Pathways That Lead to Changes in Cardiac Conduction

Eicosanoids have physiological and pathological effects on the heart, affecting both heart rate and the structural responses to hemodynamic stress.98 Dietary fatty acids can affect cardiovascular function by modulating systemic inflammatory pathways. Activation of leukocytes (especially monocytes and macrophages) promotes the release of AA, which is then metabolized into chemotactic compounds (eg, leukotriene B4, LTB4) that recruit inflammatory cells (neutrophils, monocytes) to injured tissues. The corresponding ω3 PUFA metabolite LTB4 is much less effective as a chemokine.97 Slow and heterogeneous conduction is prominent in areas with increased inflammatory cell infiltration98; however, the cellular basis for inflammatory arrhythmias is not well defined.99 In studies based on receptor knockout mice, thromboxane A2 and prostaglandin F2α (both AA metabolites) were implicated as mediators of inflammatory tachycardias.100 Increased ω3 PUFA consumption decreases the availability of AA and subsequently may modulate the production of prostaglandin E2 and other inflammatory eicosanoids.101,102 Duda et al102 reported that serum levels of tumor necrosis factor-α (TNF-α), as well as urinary thromboxane B2 and 6-keto prostaglandin F1, were elevated in a rat model of abdominal aortic banding. Dietary EPA/ DHA supplementation blunted this effect and attenuated the left ventricular remodeling and systolic dysfunction that is characteristic of the abdominal aortic banding model.102 Cardiac-specific deletion of cyclooxygenase-2 (COX-2) expression eliminates the ability to synthesize COX-2–dependent eicosanoids; these mice have a slower heart rate and increased fibrosis after aortic banding.96 Together, these studies suggest that eicosanoids are important modulators of cardiac function and arrhythmogenesis. The balance of dietary ω3 and ω6 PUFAs modulates the distribution of eicosanoids produced, thus affecting heart rate, ectopic activity, and cardiac conduction patterns.
Impact of Dietary Fatty Acids on Cardiac Fibroblasts and Intersitial Fibrosis

Arrhythmias require an initiating trigger and a substrate to become persistent. Structural remodeling, including reactive and replacement fibrosis, often underlies reentrant arrhythmias. Fibroblast expression is normally low in the healthy heart but increases in response to inflammatory stimuli and with advanced age, hypertension, hemodynamic overload, valve dysfunction, and heart failure. Multiple signaling pathways regulate the development of interstitial fibrosis, with prominent roles evident for the renin-angiotensin system, aldosterone, and cytokines, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), TNF-α, and AA metabolites. Fish oil (ω3 PUFA) has been shown to suppress endothelial PDGF formation. As fibrosis is an important determinant of arrhythmia persistence, it is not surprising that antifibrotic agents demonstrate antiarhythmic efficacy (eg, angiotensin-converting enzyme inhibitors, statins, and aldosterone antagonists).

Fibroblast proliferation and extracellular matrix accumulation is a normal and important element of wound healing. In conditions such as heart failure and myocardial infarction, fibroblasts elaborate extracellular matrix components (primarily collagen) that can provide stiffness to injured myocardium. In heart failure, fibroblast proliferation and matrix accumulation occur more rapidly in the atrial than ventricular myocardium, contributing to an increase in AF vulnerability. Myocyte interactions with myofibroblasts can promote heterogeneous conduction, because myofibroblasts typically have a less negative (more depolarized) resting potential than cardiac myocytes. Miragoli et al showed that myofibroblasts can modulate conduction velocity and ectopic activity of cardiac tissues, primarily via gap junction-mediated electrotonic interactions. In a canine model of heart failure subsequent to rapid ventricular pacing, development of atrial interstitial fibrosis has also been shown to be a critical determinant of AF episode duration. In this model, aERP was prolonged, and, after the development of atrial fibrosis, arrhythmia episode duration became independent of the electric remodeling status.

Fibrosis, Dietary Lipids, and Arrhythmogenesis

Dietary lipids are implicated in the development of cardiac fibrosis and modulate arrhythmias that are fibrosis-dependent. Aubin et al reported that rats fed a high-fat diet (42% by calories versus 12.5% in control rats) for 8 weeks became hypertensive and had evidence of reactive fibrosis; unfortunately, the composition of dietary lipids was not reported. In a comparison of 2 AF models, Sakabe et al reported that oral administration of ω3 PUFA (EPA/DHA) suppressed AF inducibility and duration in a canine model of ventricular pacing—induced heart failure; in contrast, it did not modify aERP changes resulting from 1 week of rapid atrial pacing. This result contrasts with the effects of ω3 PUFAs infusion on acute aERP changes after rapid atrial pacing. In the same canine ventricular pacing—induced heart failure model, dietary supplementation with ω3 PUFAs attenuated the development of atrial fibrosis and prevented vagally induced AF.

A recent clinical trial suggests that supplemental ω3 PUFA therapy can help to prevent perioperative AF. After coronary artery bypass graft surgery, 15% of patients randomly assigned to receive the ω3 PUFA supplement had AF, compared with 33% of the control patients. Patients who received ω3 PUFAs also had a shorter length of hospital stay. Because of the promising preclinical and clinical evidence, several randomized trials of supplemental ω3 PUFA for prevention of postoperative AF or recurrent AF are underway, seeking to confirm and extend the encouraging preclinical and clinical observations.

Summary and Conclusions

The specific composition of dietary lipids, the daily caloric intake, and the fraction of calories consumed as lipids are quite variable around the world. Epidemiological data suggest that the typical Western diet is not optimal from the perspective of cardiovascular health or longevity. The Western diet is frequently excessive with respect to total calories consumed, calories derived from sugar, and carbohydrates from saturated or trans-fatty acids. In contrast, the Western diet is often deficient with respect to ω3 PUFA content. The prevalence of cardiovascular disease and death caused by arrhythmia is increased in the United States, relative to populations consuming Mediterranean diets or those regions with greater ω3 PUFA content.

Dietary lipids can promote the development of atherosclerosis and activation of inflammatory cells. In the setting of ischemia, fatty acid metabolites can exacerbate vasoconstriction, spontaneous electric activity, and heterogeneities of repolarization and conduction (by modulating voltage-gated ion channels, gap junctions, intracellular calcium homeostasis, and ectopic electric activity). These alterations promote arrhythmogenesis. However, dietary fatty acids also can have numerous beneficial effects (Figure 3). ω3 PUFAs...
decrease the inflammatory response to injury and the development of fibrosis in the setting of heart failure. In addition, α3 PUFAs may preserve mitochondrial function by decreasing oxidant stress and subsequent inhibition of the electron transport chain. In the setting of inflammation or failure, vagal tone is preserved or enhanced, and heart rate is slowed. These effects of α3 PUFAs are anticipated to promote the maintenance of normal cardiac rhythm.

Diet affects autonomic tone. In young athletic individuals with AF, increased vagal tone may contribute to the etiology of AF; in such individuals, increased dietary α3 fatty acid intake might not be advisable. In contrast, for individuals with elements of the metabolic syndrome, changes in dietary lipid composition may lower the risk of cardiovascular disease and cardiac arrhythmia. Preventative measures, including changes such as increased α3 PUFA consumption, in combination with lifestyle changes (increased activity) may help to achieve this goal. Development of practical and effective guidelines will require additional research to determine the nature and extent of changes required and to identify optimal dietary sources of α3 PUFA.

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None.

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