

Fish oil—an appetising alternative to anti-arrhythmic drugs?

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Observational and trial data have accumulated to support the hypothesis that increased consumption of the long-chain n-3 polyunsaturated fatty acids found in fish, especially eicosapentaenoic and docosahexaenoic acids, lower the risk of dying from coronary heart disease,¹ and interest has focused on the anti-arrhythmic properties of these fatty acids. In the late 1980s, McClennan et al² were the first to show anti-arrhythmic properties associated with these fatty acids in animal models. Billman et al³ confirmed and expanded on these experiments in a dog model. Further experiments reported plausible cellular mechanisms for the anti-arrhythmic effects, including modulation of sodium, potassium, and calcium channels.⁴ n-3 fatty acids might also have favourable actions on heart rate variability, and therefore could be exerting anti-arrhythmic actions through effects on the autonomic nervous system.⁵

Burr et al⁶ published the first randomised trial of the effect of fish consumption on death from coronary heart disease, the Diet and Reinfarction Trial (DART). In DART, just over 2000 men with a history of myocardial infarction were randomised to three dietary strategies (lowering saturated fat, increasing fibre, and increasing fatty-fish intake). There was a 29% reduction in total mortality in the participants who received advice to eat at least two portions of fatty fish a week, but no difference in total events for coronary heart disease because more non-fatal myocardial infarctions occurred in the fish-advice group. To explain these apparently discordant effects on fatal versus non-fatal events, Burr et al suggested that fish consumption might reduce the risk of fatal arrhythmias, and therefore preferentially affect mortality after myocardial infarction. Siscovick et al⁷ addressed this hypothesis by studying whether dietary intake and blood levels of n-3 fatty acids were associated with risk of a primary cardiac arrest, in a retrospective population-based case-control design. In the US Physicians' Health Study,^{8,9} we investigated the same questions with respect to sudden cardiac death in a prospective cohort of over 20 000 apparently healthy US male physicians. Both studies showed relative-risk reductions of about 50% in risk associated with an intake of one fish-meal a week, and even more striking reductions of 81–90% in those with blood concentrations of n-3 fatty acid in the top quartile. We also studied non-fatal myocardial infarction and, similar to the DART trial, saw no benefit on this endpoint.^{8,10}

Perhaps the most compelling clinical evidence to date for an anti-arrhythmic mechanism of action of the long-chain n-3 polyunsaturated fatty acids comes from the largest randomised trial, the GISSI-Prevenzione Trial.¹¹ Over 11 000 patients surviving a recent myocardial infarction were assigned at random, in an unblinded fashion, to fish oil and/or vitamin E in a two-by-two factorial design. The patients assigned to fish oil had a significant reduction in the primary endpoint (death, non-fatal myocardial infarction, and non-fatal stroke) due to a statistically significant reduction in total mortality (20%). Again, as in DART, there was no benefit on non-fatal cardiovascular events. When investigated further, much of the benefit on mortality was attributable to a 53% reduction in sudden cardiac death that emerged at 4 months of follow-up.¹²

In this issue of *The Lancet*, Rainer Schrepf and colleagues report an important addition to the evidence about the anti-arrhythmic properties of the long-chain n-3 fatty acids. These investigators present the first, albeit preliminary, data on the acute anti-arrhythmic effects of long-chain n-3 fatty acids in human beings. Patients with implantable cardioverter defibrillators, who had ventricular tachycardia at preimplant electrophysiological testing and repeated episodes of ventricular tachycardia, underwent subsequent non-invasive electrophysiological testing. Nine of the ten patients were men, had underlying coronary heart disease, and a history of sustained ventricular tachycardia and/or fibrillation. Of the ten patients who underwent testing, seven had monomorphic sustained ventricular tachycardia induced. Of these, five patients were rendered non-inducible after an intravenous infusion of 3.8 g n-3 polyunsaturated fatty acids. In addition, like many anti-arrhythmic drugs, the fish-oil infusion prolonged the ventricular effective refractory period, a measure of myocardial excitability. As recognised by Schrepf and colleagues, the possibility that variability in the results of electrophysiological testing, rather than a true anti-arrhythmic effect of the n-3 fatty-acid infusion, cannot be excluded and could provide an alternative explanation for the results. However, the immediate reproducibility of monomorphic ventricular tachycardia induced during invasive electrophysiological testing is high, ranging from 77 to 98%,¹³ which argues against this alternative as the sole explanation. Without a placebo group and a blinded randomised comparison, it is also impossible to exclude the possibility that chance accounts for the results in this small sample. Regardless, these preliminary data do not seem to demonstrate a pro-arrhythmic effect and support a possible anti-arrhythmic effect of these fatty acids.

What are the implications of these findings? As has been shown with traditional anti-arrhythmic drugs, suppression of ventricular tachycardia during electrophysiological testing does not directly translate into a survival benefit when the same drugs are administered chronically.¹⁴ Therefore the implications of these data on their own are limited. However, Schrepf and colleagues' findings, in conjunction with previous experimental data, provide a possible mechanism to explain the preferential benefit seen with dietary intake of n-3 fatty acids on sudden cardiac death in the earlier observational studies and randomised trials. These preliminary data need to be confirmed in randomised trials with hard arrhythmic endpoints in combination with mortality. Currently, three such randomised trials of the effect of fish-oil supplementation on recurrent episodes of ventricular tachycardia and/or fibrillation in patients with implantable cardioverter defibrillators are in progress or have been completed. If these and other trials confirm the anti-arrhythmic pro-

properties of these n-3 acids, fish oil might become a less toxic and more appetising alternative to traditional anti-arrhythmic drugs.

I have no conflict of interest to declare.

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