Review Article

The role of omega-3 polyunsaturated fatty acid-enriched diets in the prevention of ventricular fibrillation

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In a number of epidemiological surveys and in two recent intervention trials in cardiac patients, diets rich in marine omega-3 polyunsaturated fatty acids (PUFA), which include both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been found to be beneficial in reducing the susceptibility of developing serious ventricular fibrillation (VF) or malignant cardiac dysrhythmia and mortality from sudden cardiac death (SCD). In addition to this information from human studies, there is strong supporting evidence from laboratory experiments utilizing the small non-human primate marmoset monkey (*Callithrix jacchus*). For example, a diet enriched with tuna fish oil that is high in both DHA and EPA has been found to increase the electrical threshold current necessary for inducing VF and to reduce mortality to zero in marmoset monkeys with experimentally induced ischaemic cardiac dysrhythmia (ICH). From these and earlier studies in other animals there is also some evidence which suggests that it may be the DHA rather than the EPA component of fish oils which is the biologically active fatty acid responsible for the reduction in susceptibility of developing VF and ICH. If this possibility could be determined with confidence, it would greatly assist in the design of future intervention trials, which are required in order to determine both the nature and amount of dietary omega-3 PUFA that is necessary to achieve these beneficial effects. Any simple dietary strategy that could lead to a substantial decrease in VF and mortality from SCD would be of great medical, social and economic benefit.

Key words: omega-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid, docosahexaenoic acid, ventricular fibrillation, sudden cardiac death

Introduction

Recently, the American Heart Association re-affirmed that more than 250 000 sudden cardiac deaths (SCD) occur in the USA every year.[1] Generally, SCD are defined as occurring within 1 hour of the onset of symptoms and at least half of the individuals have no previous history of heart disease.[2,3] Apparently a very similar situation exists in other countries such as Australia and the United Kingdom.[4,5] It is therefore not surprising that SCD has been described as the most common mortal event in affluent societies and that any simple preventative measure that could be developed would be of immense medical and social benefit.[6] While a reduction in dietary saturated fats (SF) accompanied by an increase in polyunsaturated fatty acids (PUFA) is widely recommended in order to reduce the risk of all forms of cardiovascular disease (CVD), it is only recently that a more specific role for long-chain omega-3 PUFA has been recognized as a major factor in the prevention of ischaemic arrhythmia and consequently SCD.[7,8]

Although the role of eicosapentaenoic acid (EPA; 20C:5) in platelet aggregation and thrombosis is well established,[9] the concept that the longer-chain more highly unsaturated 22-carbon omega-3 PUFA docosahexaenoic acid (DHA; 22C:6) might have a specific role in the prevention of sustained ventricular fibrillation, cardiac arrhythmia and SCD in both humans and animals is only currently under consideration.[7,10] However, it is more than 25 years since Nelson first reported a significant decrease in mortality from 'coronary disease' among those of his patients who consumed a carefully prescribed diet rich in fish containing DHA.[11] That this result could be observed within 6 months of commencement of the diet was seen by Nelson as being of major importance in patient compliance but was attributed to a reduction in blood cholesterol and an increase in the patient's phospholipid fatty acids, rather than any specific metabolic effect of DHA.

The low death rate from coronary heart disease (CHD) in Greenland Eskimos observed by Bang *et al.*[12] and the inverse relationship between fish consumption and CHD in middle-aged men in the Netherlands reported by Kromhout *et al.*[13] were thought to be due to the anti-atherosclerotic action of EPA, which reinforced the benefits of including omega-3 PUFA rich oily fish in the diet. The latter results were observed following only a comparatively small daily intake of oily fish and could not be fully explained by the effect of such a low amount of EPA on either platelet aggregation or bleeding time. Apparently, a possible direct effect of DHA was not considered in these studies, although DHA makes up as much, if not more, of the total omega-3 PUFA content of many so-called oily fish.[11] In addition, the rapidity of the decrease in mortality from ischaemic heart disease (IHD) which occurred in Norway during the period of 1940–45, when the consumption of total omega-3 PUFA as fatty fish suddenly trebled, and the equally 'explosive post-war increase' in IHD which occurred following the reintroduction

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of meat and dairy products to the diet, again reinforced the beneficial effects of these fatty acids on CHD.[14,15] However, the rate of change of these dietary effects, both beneficial and detrimental, was thought to provide evidence against the involvement of atherosclerosis and/or thrombosis in the marked alteration in morbidity from IHD during this period.[16]

Epidemiological surveys

Subsequently, Burr *et al.* reported the results of their Diet and Reinfarction Trial (DART), in which over 1000 post-myocardial infarction (MI) men with a mean weekly intake of approximately 300 g fatty fish over a 2-year period were found to be much less likely to die from fatal myocardial reinfarction than another reference group of equal size and clinical history who did not eat fish at all.[17] This level of fatty fish intake was estimated to provide approximately 2.3 g of EPA (and presumably an approximately equal amount of DHA) and was thought to represent the amount of omega-3 PUFA that might be expected from one or two meals of fatty fish per week. Burr *et al.* observed that significant differences in the rates of mortality were apparent between dietary groups in less that 100 days from the commencement of the trial, and reached approximately 30% after 6 months. Neither the total serum cholesterol nor the HDL cholesterol of the subjects eating fish (or in some subjects a fish oil supplement) were significantly different from those in other groups at either the 6-month or 2-year examination point in the trial.[17]

As the incidence of reinfarction was not significantly reduced in the omega-3 PUFA dietary supplemented group, Burr and Fehily, in a later paper, suggested that the benefit of the 'fish diet' in post MI men may be attributed to a possible decrease in fatal ischaemic dysrhythmia, rather than a reversal of some atherosclerotic process.[18] Not surprisingly, these conclusions generated considerable debate at the time and are still the subject of vigorous discussion.[19,20]

In their analysis of data from the Multiple Risk Factor Intervention Trial (MRFIT), Dolecek and Grandits reported that the estimated mean intake of total omega-3 PUFA was only 175 mg/day, and that even this relatively low level of intake was subject to considerable variability, with approximately 20% of the subjects reporting zero intake.[21] After exclusion of deaths from myocardial infarction during the first 3 years follow-up period, Dolecek and Grandits reported that both CHD and CVD mortality were lowest in the group that ingested the highest intake of omega-3 PUFA, which was calculated to be approximately 650 mg/day. This inverse relationship between CHD and CVD mortality and omega-3 PUFA intake supported the earlier observations of Bang and Dyerberg[22] and Gottman,[23] who reported a similar relationship between a high intake of marine omega-3 fatty acids and a low incidence of acute myocardial infarction in Greenland Eskimos and Alaskan natives, respectively.

In their more recent case-control study, Siscovick *et al.* observed that an intake of one fatty fish meal/week (estimated to contain 5.5 g of omega-3 PUFA made up of EPA and DHA) resulted in a 50% reduction in the risk of primary cardiac arrest.[24] By using red-cell membrane omega-3 PUFA as a marker, they noted that when the level of omega-3 PUFA reached 5% of the total red cell membrane fatty acids, the reduction in risk of primary cardiac arrest was 70%. However, a 30% decrease was apparent even at the lowest level of omega-3 PUFA intake (2.9 g omega-3 PUFA), which they stated was equivalent to 'only two fish meals per month'.[24] These investigators suggested that the positive effect of omega-3 PUFA was more likely to occur through a reduction in vulnerability of the myocardium to ventricular fibrillation and thereby mortality from SCD than through any other causes of coronary heart disease, such as an alteration in serum lipid profiles.

More recently, Albert *et al.* reported their analysis of the relationship between fish consumption and the risk of sudden cardiac death determined from the data acquired in the US Physicians' Health Study.[25] A beneficial effect was observed both at a low level of intake (two fatty fish meals per month) or at higher levels of 1–5 fish meals per week. However, as there was no apparent dose–response relationship between intake and effect, it is possible that an even lower threshold level of omega-3 PUFA was sufficient to produce the response that was reported.[26]

Albert *et al.* also acknowledged that an alternative dietary source of omega-3 PUFA may have obscured the determination of either a threshold or dose-related effect of omega-3 PUFA. It is therefore unfortunate that, unlike the previous study of Siscovick *et al.*,[24] no actual marker of tissue omega-3 PUFA was presented in their analysis of the data from the US Physicians' Health Study, particularly as alpha-linolenic acid (ALA, 18C:3), which is a precursor to EPA and DHA, has been shown to be beneficial in reducing death from heart disease in humans.[27] In addition Seibert *et al.*[28] and McLennan and Dallimore[29] have shown that canola oil, which contains approximately 10% ALA, is effective in reducing ischaemic arrhythmia in rats.

It seems very likely that at least some dietary ALA would have been available to the participants in this US Physicians' Study as it was conducted over an 11-year period. Notwithstanding these limitations, the authors' conclusion that although 'fish consumption was not a marker for a lower risk of myocardial infarction, any intake of (marine) omega-3 fatty acid was associated with a decreased risk of sudden cardiac death,' seems to be quite reasonable and certainly agrees with the conclusion of Burr *et al.* from their findings in the DART intervention trial.[17,18]

Intervention studies

In addition to these epidemiological surveys, there have been two recent attempts to directly determine the effect of added omega-3 PUFA intake on the extent of ventricular extrasystoles in hospital patients exhibiting tachycardia and thought to be at risk of developing serious cardiac arrhythmia. In the first of these studies Christensen *et al.* administered fish oil capsules with a combined EPA and DHA content of 4.3 g/day for a period of 16 weeks.[30] The 'control' group received a corn oil supplement rich in omega-6 PUFA. The number of extrasystoles over a 48-h period was recorded at the beginning and end of the trial. Both omega-3 and omega-6 PUFA supplements resulted in marked falls in extrasystoles (95% and 43%, respectively) over the test period. Unfortunately the relatively small number of patients in each group and the variance in determining mean values of extrasystoles prevented the establishment of statistical significance between

groups, although an increased trend towards reduced ventricular extrasystoles in the omega-3 group was apparent.

This result is not surprising since both omega-3 and omega-6 PUFA dietary supplements have been shown to be effective in maintaining relatively high threshold currents for ventricular fibrillation in experiments with non-human primates.[31,32] On the basis of this experimental evidence in a non-human primate, plus a large body of additional information obtained in other species, it is evident that the omega-6 PUFA 'control' supplement employed by Christensen *et al.* cannot be considered to be inert.[33]

A similar 16-week study by Sellmayer *et al*. was carried out in a cardiac out-patient hospital.[34] All of the patients involved had a history of frequent ventricular premature complexes (VPC) and left ventricular ejection fractions of less than 40%, which is known to be an added risk factor in the development of ventricular arrhythmia and SCD.[35] In addition, many patients were already receiving treatment with anti-arrhythmic drugs which were continued throughout the trial period. One group received 15 mL of cod liver oil containing 0.9 g EPA and 1.5 DHA daily, while an alternative group was given sunflower seed oil which contained 5.0 g of the omega-6 PUFA linoleic acid (LA; 18C:2) as a placebo. Serum phospholipid fatty acids were measured at the start and completion of the study.

In the cod liver oil-fed group, EPA rose from 1.3% to 2.8% of the total serum fatty acids and DHA from 3.6% to 5.5%, but LA and its major metabolite arachidonic acid (AA; 20C:4) did not change significantly. The mean VPC were shown to decrease by 48% in the cod liver oil-supplemented group compared with only a 25% reduction in the group who received the sunflower seed oil supplement. Despite the large standard errors that were again found in the determination of mean VPC values, and the use of LA-rich sunflower seed oil as a placebo (which cannot be considered to be any more inert than the corn oil control employed by Christensen *et al.*),[30] the authors concluded that dietary supplementation with a moderate dose of 'fish oil' has an anti-arrhythmic effect even in patients already undergoing anti-arrhythmic drug therapy.[34]

Unfortunately, both of these intervention trials really only compare the effectiveness of one class of PUFA dietary supplement against another and certainly do not permit the determination of whether it is either EPA or DHA (or both omega-3 PUFA) which might be the effective agent in reducing myocardial susceptibility to VF. A direct comparison of DHA or EPA versus a truly arrhythmogenically inert placebo might resolve this question. The monounsaturated oleic acid (18C: 1) in olive oil may be a suitable control as it has been found to be without anti-arrhythmic properties in studies in rats.[36] However, to our knowledge this has not been tested as yet in either non-human primates or in humans. Nevertheless, it is of interest to recall that the human autopsy data of Gudbjarnasson *et al.*,[37,38] which was reported approximately 20 years ago, showed that the level of DHA (but not EPA) in the heart muscles of people who died suddenly either at home or at work from 'heart disease' was less than that of other individuals of similar age who died suddenly in road or other fatal accidents but who did not have similar 'heart disease'.[39]

Animal experiments

In addition to these observations in humans there is also some pertinent experimental data available from controlled dietary studies employing the small non-human primate marmoset monkey. These animals have been shown to be very suitable for studies of essential fatty acid metabolism, prostanoid production, myocardial cellular biochemistry and cardiac function as they yield results which are very similar to those obtained in humans.[40–44]

With regard to the vulnerability of the heart to develop ventricular fibrillation when under either ischaemic or catecholamine-induced stress, McLennan *et al.* have used programmed electrical stimulation of the myocardium *in situ* to show that both omega-6 and omega-3 PUFA-enriched diets lead to significant increases (≥ 50%) in the ventricular fibrillation threshold (VFT) compared with those found in marmosets fed either a saturated animal fat supplement or a nutritionally adequate 'low fat' diet containing mixed fats of both plant and animal origin.[31] As in humans, the VFT was reduced in all dietary groups during a period of regional ischaemia, which in the laboratory was induced by ligation of a major coronary artery.

The beneficial effect of PUFA-enriched diets was even more apparent under ischaemic conditions, as the increase in the VFT was now more than 75% greater than that in the group which had received a saturated animal fat dietary supplement. This benefit was also apparent during an infusion of isoprenaline where the VFT was again significantly greater in the PUFA-fed animals than in the other dietary groups. However, in contrast to the omega-6 PUFA-fed group, only the animals which had received the omega-3 PUFA-enriched diet displayed a low incidence of sustained fibrillation episodes and no fatalities under conditions of catecholamine stress.[31] In confirmation of these results, McLennan *et al.* subsequently demonstrated that even when mixed with saturated fats, a much smaller amount of dietary omega-3 PUFA than that employed in their earlier experiments was capable of producing a significantly elevated VFT compared with that found after feeding a mixed omega-6 PUFA, saturated animal fat diet.[32] This effect was found in both the normal and ischaemic myocardium of marmoset monkeys.

At the conclusion of these studies it was possible to demonstrate that the myocardium of the omega-6 PUFA-fed group contained abundant LA and AA, but little EPA or DHA. However, the myocardium of the omega-3 PUFA-fed group contained much less LA and AA, but significantly greater amounts of EPA and DHA. Consequently, the omega-6/omega-3 PUFA ratio of the myocardial muscle membranes was reduced from 3.3 to 0.8.[45] Subsequent examination of the fatty acid composition of many other tissues of the marmosets, including brain, kidney, plasma and adipose tissues as well as skeletal and myocardial muscle, revealed that although the brain is usually considered to accumulate DHA in preference to EPA, the muscle tissues were even more active in this regard.[46,47] However, this was only apparent when a source of omega-3 PUFA was provided in the diet as, apart from blood red cell membranes, almost no other tissue of the marmoset contained any EPA at all, and only comparatively low levels of DHA. As a consequence of this, it is probable that a biopsy sample of human skeletal muscle could provide an accurate assessment of myocardial fatty

acid composition, whereas analysis of blood (red cell membrane) or adipose tissue samples markedly underestimate myocardial omega-3 PUFA levels.

Conclusions

The accurate estimation of different cardiac muscle omega-3 PUFA values may be of great clinical significance as very recently McLennan *et al.* reported that DHA, but not EPA, in very low doses inhibits ischaemic cardiac arrhythmia in rats.[47] This lends support to the hypothesis that while EPA is known to be responsible for the anti-aggregatory and antithrombotic properties of omega-3 PUFA contained in most fish oils, it is perhaps the DHA component of these oils which is responsible for the anti-arrhythmic properties of fatty fish diets. It is of interest that in his recent discussion of omega-3 fatty acids and their inhibition of endothelial activation, Caterina also raises the possibility that EPA and DHA may not share a 'similar spectrum of biological and pharmacological profiles' and that 'biologically important differences … may exist in the action of these two compounds'.[48] However, whether it be DHA or EPA that is the active component of fish oil, there is considerable evidence that the consumption of omega-3 PUFA-enriched diets leads to a marked reduction in the susceptibility of the myocardium to develop ventricular fibrillation and subsequent SCD.

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