CARDIOLOGY Rounds®

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Omega-3 Polyunsaturated Fatty Acids (Fish Oils) and Heart Disease – Clinical Benefit or Just a Fad?

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The effect of marine-derived fish oils (omega-3 [Ω-3] polyunsaturated fatty acids [PUFAs]) on human health and disease continues to fascinate researchers in many disciplines. A PubMed search (http://www.ncbi.nlm.nih.gov/sites/entrez) in July 2008 revealed a total of 11,000 articles relating to the effects of "PUFAs, EPA, or DHA" on health. Despite decades of research on the various putative health benefits of a diet rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), believed to be the most important Ω-3 PUFAs contained in fish oils, and the approval of the United States Food and Drug Administration for EPA and DHA as having a qualified health claim for coronary heart disease reduction,[1] there is incomplete consensus on the overall benefits of diets enriched with Ω-3 PUFAs. Different opinions exist on the types of diseases that could potentially be prevented or treated by such dietary enrichment or supplementation, and the potential mechanisms of benefit are particularly in doubt.[2] The lack of clarity on clinical benefit is underscored by the large number of ongoing randomized controlled trials (RCTs) on the effect of Ω-3 PUFAs on cardiac disease (as well as other diseases); as of July 2008, there were at least 246 clinical trials involving Ω-3 PUFAs registered on www.clinicaltrials.gov. Disease conditions under investigation with Ω-3 PUFAs vary widely from mental health disorders, to cancer, to cardiovascular (CV) disease. This issue of *Cardiology Rounds* reviews the issues and evidence surrounding the debate on Ω-3 PUFAs in heart disease.

Nutritional biochemistry of PUFAs

Long-chain polyunsaturated fatty acids (PUFAs) are necessary for human health, particularly the functioning of cellular membranes. Humans ingest fatty acids from plant and/or animal sources, and these are metabolized by successive elongation and desaturation reactions to manufacture biologically active components.[3,4]

PUFAs of the Ω-3 and Ω-6 series are so called "essential" fatty acids since they are not synthesized by man and must be provided in food, primarily in the form of vegetable or animal fat based oils. Some of the most common examples are: Ω-6 linoleic acid (LA) derived from corn, peanut, and sunflower oils (but also found in animal meat); Ω-3 α-linolenic acid (ALA) derived from flaxseed, canola, linseed, and soybean oils; and finally, the Ω-3 PUFAs, EPA and DHA, found in the fatty tissue of cold water fish such as salmon, cod, mackerel, herring, and sardines (as well as the animals that consume these fish).

Organisms vary in their ability to convert one form of PUFA into another. Marine algae and phytoplankton metabolize LA into ALA and then to EPA and DHA (hence the high quantity of EPA and DHA in the cold water fish that feed on these organisms). In contrast, human conversion from ingested ALA to EPA is only 0.2%-15% efficient,[1] and very little, if any, DHA is produced by humans through dietary conversion.[4] However, humans do convert LA into the Ω-6, arachidonic acid (AA) quite efficiently (Figure 1).

AA and EPA (and to some extent DHA), sit atop a complex cascade of metabolic pathways where they compete for enzymes that will convert them into their respective end products termed eicosanoids. Interaction with cyclooxygenases (COX-1 or COX-2) produces prostanoids (prostaglandins, prostacyclins, and thromboxanes). Interaction with lipoxygenase (5-lipoxygenase) produces leukotrienes.[5] Products derived from AA include proinflammatory and proplatelet

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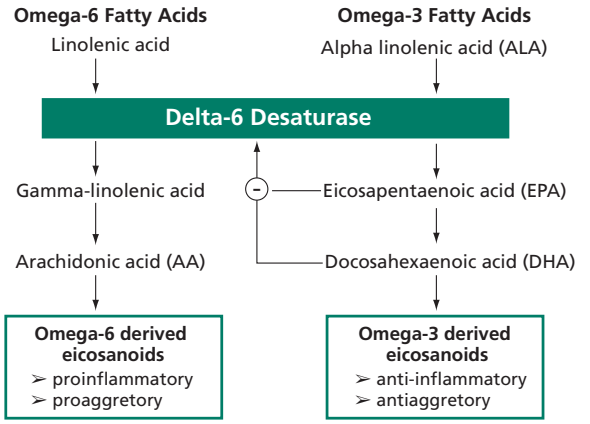
Figure 1: Fatty acid metabolism



Θ = feedback inhibition

aggregating eicosanoids (eg, thromboxane A2), whereas products derived from EPA tend to be anti-inflammatory and antiplatelet aggregating (eg, thromboxane A3).[6] The metabolism of DHA follows similar pathways and produces products termed docosanoids or eicosanoid-like products. Examples include various anti-inflammatory protectins and resolvins.

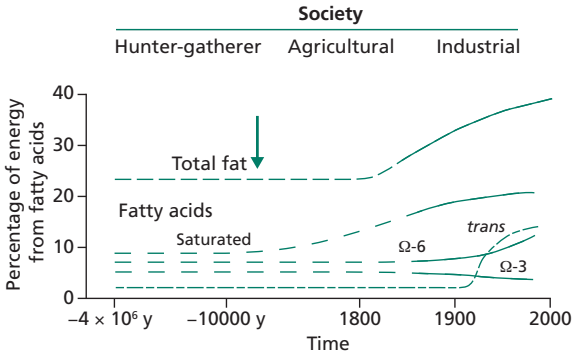
PUFAs in the human diet

Commonly obtained sources of Ω-3 PUFAs in the North American diet include fatty fish such as salmon, mackerel, and herring; these fish have a 1:1 ratio of Ω-3 to Ω-6. However, not all fish are necessarily high in these potentially beneficial fatty acids. For example, in farm-raised tilapia the EPA to AA ratio is 1:11.[7] Estimates of Paleolithic diets suggest that early humans consumed diets containing approximately equal amounts of Ω-3 and Ω-6, as well as much lower levels of saturated and trans fatty acids compared with current dietary patterns (Figure 2).[6] In contrast, current Western diets have an Ω-3 to Ω-6 ratio of about 1:20-30.[3]

Clinical and epidemiologic studies with PUFAs

Epidemiological observations in Greenland Eskimos and other populations with diets extremely high in fatty fish indicate that they rarely develop coronary disease.[8] Subsequent epidemiological studies have strongly suggested that eating a diet high in fatty fish containing EPA and DHA, or the ingestion of fish oil capsules, is associated with a lower risk (than with standard Western diets) for the development of coronary disease and its complications. Landmark studies, such as the Diet and Reinfarction Trial (DART)[9] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-3 post-myocardial infarction (MI) trial,[10] suggested that dietary or direct (in capsule form) EPA + DHA supplementation could reduce cardiac mortality, complications of coronary artery disease (CAD) and, particularly, sudden cardiac death (SCD) compared with controls. In a recent trial from Japan[11] (where fish consumption is likely high), 18 645

Figure 2: Estimated fat and fatty acid consumption patterns for prehistoric and historic human societies[6]

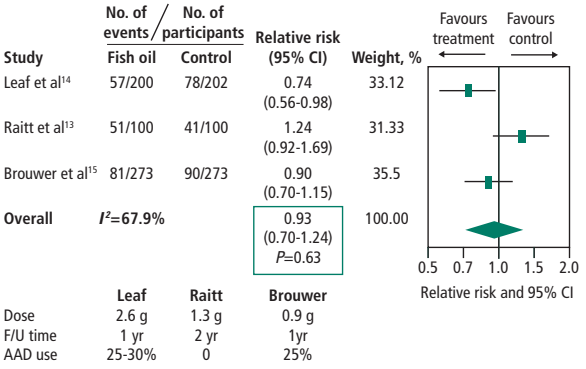


patients were randomized to 1800 mg/day EPA plus a statin vs a statin alone; major coronary events and unstable angina were significantly reduced by 19% and 24%, respectively (with no effect on SCD). Benefits from EPA were found in patients with and without prior coronary heart disease. This study suggests that PUFA benefits can be demonstrated even in populations with a low risk of CAD, high fish consumption, and are additive to the benefits from statins.

Based on these studies, the American Heart Association recommends fatty fish consumption more than twice a week, or if not feasible, supplementation with Ω-3 fish oil capsules (about 1 g DHA + EPA /day)[1] for primary or secondary prevention of CV disease and its complications.

However, other epidemiological studies have failed to demonstrate a protective effect of Ω-3 PUFAs on CV mortality or CV outcomes and, in some cases, the intervention studies seem to show harm. In DART-2,[12] PUFA supplementation in patients with angina led to a 26% increase in mortality. There have also been 3 negative placebo-controlled, randomized trials of Ω-3 PUFAs in the prevention of ventricular tachyarrhythmias in patients with prior ventricular tachycardia (VT) or ventricular fibrillation (VF), and implanted cardioverter defibrillators (ICDs).[13-15] In each

Figure 3: Meta-analysis of ICD discharge in studies on fish oil supplementation[51]



AAD = antiarrhythmic drug; ICD = implanted cardioverter defibrillator

Table 1: Baseline characteristics of patients in GISSI-HF[21]

Patients' characteristics	Ω-3 PUFA (n=3494)	Placebo (n=3481)
Age (years)	67 (11)	67 (11)
Age >70 years	1465 (41.9%)	1482 (42.6%)
Women	777 (22.2%)	739 (21.2%)
Heart disease risk factors		
BMI (kg/m^2)	27 (5)	27 (5)
SBP (mm Hg)	126 (18)	126 (18)
DBP (mm Hg)	77 (10)	77 (10)
Heart rate (beats per min)	72 (13)	72 (14)
Currently smoking	502 (14.4%)	485 (13.95)
History of hypertension	1886 (54.0%)	1923 (55.2%)
NYHA class		
II	2226 (63.7%)	2199 (53.2%)
III	1178 (33.7%)	1187 (34.1%)
IV	90 (2.6%)	95 (2.7%)
LVEF (%)	33.0% (8.5)	33.2% (8.5)
LVEF >40%	333 (9.5%)	320 (9.2%)

Data are mean (SD) or number (%). GISSI-HF = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Heart Failure; PUFA = polyunsaturated fatty acids; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction.

of these studies, there was no significant reduction in appropriate defibrillator therapy for VT or VF in the EPA+DHA groups (Figure 3). These trials suggest that considering PUFAs as straightforward "antiarrhythmic" drugs is not applicable *in vivo*. In a meta-analysis,[16,17] Ω-3 PUFAs were ineffective in preventing restenosis after angioplasty.

Recent reviews[18-20] have highlighted this incomplete understanding of the benefits from Ω-3 PUFAs in cardiac disease. In 2004, the Agency for Healthcare Research and Quality (AHRQ) reviewed all Ω-3 PUFA studies up to 2004; the AHRQ identified 11 randomized controlled trials (RCTs) and 1 cohort study of secondary prevention, and 22 cohort studies and 1 RCT of primary prevention.[2] They concluded that Ω-3 PUFAs appear protective, but numerous important research questions remain. A recent Cochrane review concluded that PUFAs did not have a clear effect on combined CV events.[20]

To summarize this extensive literature on Ω-3 PUFAs, it is likely that there are CV benefits to fish consumption or direct Ω-3 PUFA supplementation, but the specific disorders modified, the doses and timing of supplementation and, in particular, the manner in which PUFAs exert their beneficial effects are poorly understood.

The GISSI Heart Failure Trial

Understanding of the potential benefits of Ω-3 PUFAs was considerably advanced with the recent publication of this trial involving the effects of Ω-3 PUFAs in patients with heart failure.[21] This randomized, double-blind, placebo-controlled trial examined the effect of the administration of

Table 2: Baseline medical treatment in GISSI-HF[21]

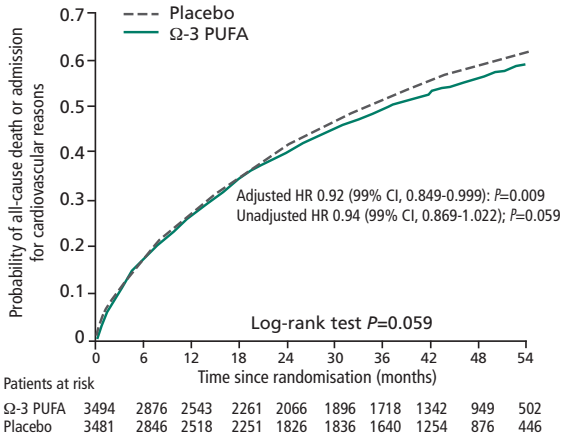
Medical treatment	Ω-3 PUFA (n=3494)	Placebo (n=3481)
ACE inhibitors	2696 (77.2%)	2678 (76.9%)
ARBs	673 (19.3%)	648 (18.6%)
Ace inhibitors/ARBs	3268 (93.5%)	3252 (93.4%)
B blockers	2275 (65.1%)	2247 (64.6%)
Spironolactone	1347 (38.6%)	1393 (40.0%)
Diuretic drugs	3127 (89.5%)	3133 (90.0%)
Digitalis	1296 (37.1%)	1292 (37.1%)
Oral anticoagulant drugs	1027 (29.4%)	982 (28.2%)
Aspirin	1673 (47.95)	1685 (48.4%)
Other antiplatelet drugs	345 (9.9%)	371 (10.7%)
Nitrates	1236 (35.4%)	1236 (35.5%)
Calcium channel blockers	343 (9.8%)	366 (10.5%)
Amiodarone	668 (19.1%	690 (19.85)
Statin	778 (22.3%)	801 (23.0%)

Data are mean (SD) or number (%). PUFA = polyunsaturated fatty acids.
ACE = angiotensin-converting enzyme. ARBs = angiotensin receptor blockers.
*Available for 6899 patients (3455 Ω-3 PUFA, 3444 placebo).

1 g/day of Ω-3 PUFAs (n=3494) versus placebo (n=3481) in patients with chronic heart failure and New York Heart Association (NYHA) functional class II-IV. The baseline patient characteristics and baseline medical treatments are indicated in Tables 1 and 2.

The authors of this study concluded that there were some minor benefits to be gained in terms of all-cause mortality (Figure 4) and hospital admissions with the use of Ω-3 PUFAs. The important secondary outcomes included CV deaths, which were reduced by 10% (hazard ratio [HR]=0.90; 95% confidence interval [CI] 0.81-0.99; *P*=0.045) and hospital admission for a CV reason

Figure 4: GISSI-HF Trial – Kaplan-Meier curve for time to all-cause death or admission to hospital for CV-related reasons[21]



(HR=0.93; 95% CI, 0.87-0.99; P=0.026); however there were no significant effects on fatal and nonfatal MI, or fatal and nonfatal stroke.

Potential mechanism of Ω-3 PUFA effects

Ω-3 PUFAs reduce serum triglyceride levels, but have inconsistent effects on low-density lipoprotein (LDL) levels; at higher doses they decrease platelet adhesiveness and prolong bleeding times. EPA and DHA in combination slow heart rate,[22] increase heart rate variability,[23] and thus may exert a parasympathetic effect; this effect may indirectly lead to a decrease in inflammation in response to tissue injury.[24] Okeefe et al[25] observed that approximately 800 mg of Ω-3 PUFAs daily over 4 months significantly reduced heart rate, increased heart rate variability, and accelerated heart rate recovery after exercise. In addition, EPA and DHA reduce blood pressure,[26] systemic markers of inflammation,[4] and improve arterial compliance and ventricular diastolic filling.[27-32] They appear to improve endothelial function in some, but not in all studies;[33-38] however, they do not reduce C-reactive protein levels.[37,38] *In vitro*, EPA and DHA have ion channel-blocking effects. Leaf[14] and Mozaffarian[22] suggest that EPA and DHA may exert antiarrhythmic benefits by their ability to block sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) channels *in vitro*; they also reduce ischemia and reperfusion-related ventricular arrhythmias in experimental models.[39]

In a meta-analysis of 36 trials studying the effect of fish oil on blood pressure (BP), fish-oil intake led to an average 3.5 mm Hg drop in systolic BP and a 2.5 mm Hg drop in diastolic BP among adults aged >45 years.[27] Mozaffarian et al[22] analyzed 30 trials testing the effect of Ω-3 PUFAs on heart rate and found a 2.5 beats/minute reduction of resting heart rate among individuals with a baseline heart rate >69 beats/minute.

Based on these observations, the mechanisms behind the effect of PUFAs on CV disease proposed in the literature include a direct antiarrhythmic effect, a decrease in vascular resistance and BP, a decrease in heart rate and an increase in parasympathetic tone, an anti-inflammatory effect, and an improvement in endothelial cell function.

These mechanistic hypotheses may be incomplete and, particularly, the hypotheses regarding antiarrhythmic effects may be incorrect. Na^+ and Ca^{2+} channel blockade, which is advanced as the likely mechanism of benefit in animal and *in vitro* studies, is not commensurate with the well-documented proarrhythmic effects of Na^+ and Ca^{2+} channel blockade in ischemic and myopathic settings.[40] The effects are also not consistent with the previously mentioned studies in patients with ICDs where Ω-3 PUFAs do not show any clinical antiarrhythmic benefits.[13-15] Most animal studies examine Ω-3 PUFA effects in left anterior descending (LAD) coronary artery ligation and reperfusion models,[39] or after intravenous infusion during acute cardiac ischemia.[41] These models have limitations for the assessment of potential benefits with long-term Ω-3 PUFA administration in the secondary prevention of coronary disease and its complications.

Effects of PUFAs on atrial fibrillation

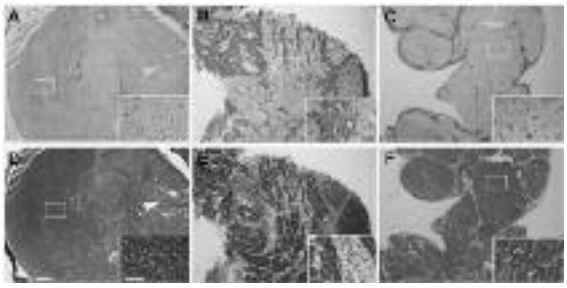
Epidemiological studies relating fish intake and blood levels of PUFAs to incident atrial fibrillation (AF) have revealed contradictory results. The Cardiovascular Health Study[42] followed 4815 persons with varying fish intake, and found a 31% risk reduction in AF between the group eating fish >5 times/ week vs <once-a-month. Other studies[43,44] of diets or PUFA blood levels did not find this association. Only 2 controlled clinical trials are available. In one RCT, 5 days of EPA + DHA (2 g/day) prior to open heart surgery led to a 65% reduction in postoperative AF.[45] On the other hand, an abstract report of PUFA treatment started 4 weeks prior to cardioversion did not show a reduction in AF recurrence at 1 year.[46] There are currently 10 ongoing trials of PUFAs (dietary or direct supplementation) investigating the effects on incident or recurrent AF (www.clinicaltrials.gov).

In animal models of AF, EPA + DHA substantially reduce the inducibility of AF; this has been demonstrated in ventricular pacing models of AF, vagal stimulation-induced AF,[47] and in a model of simultaneous atrial and ventricular pacing (the SAVP model), but not after atrial pacing alone. Studies at St. Michael's Hospital,[48] using pretreatment with approximately 840 mg (total) of EPA + DHA/day, and in the laboratory of Dr. S. Nattel at the Montreal Heart Institute,[49] using 5.3 g of EPA + DHA/day, have suggested that dietary Ω-3 PUFAs act by a previously unrecognized mechanism, ie, the prevention of stretch and dilatation-induced fibrosis, rather than by a "direct antiarrhythmic" effect. In dogs subjected to rapid ventricular pacing (which causes heart failure with ventricular enlargement, subsequent atrial enlargement, and a propensity to inducible AF), Ω-3 supplementation reduces AF inducibility, attenuates atrial fibrosis, and reduces fibrosis-related conduction slowing and hemodynamic dysfunction. Following EPA + DHA (compared to control), increases in concentrations of the phosphorylated mitogen-activated protein (MAP) kinases extracellular signal-regulated kinase (ERK; p42 and p44 isoforms) and p38 were attenuated and/or returned to control levels.[49] These effects are not seen in a rapid atrial pacing model of AF that generates shortening of atrial refractory periods, but much less atrial fibrosis.[49] Concentrations of collagen and matrix metalloproteinase-9 are also returned to control levels, indicating an antifibrotic and antiremodelling effect of Ω-3 PUFAs.[48]

These animal studies suggest that Ω-3 PUFAs act by the previously unrecognized mechanism of preventing cellular fibrosis and hypertrophy, considered hallmarks of "structural remodeling" after mechanical stress.

Figure 5: Antifibrotic effect of EPA + DHA in atrial remodeling paced by mechanical stress[48]

Unpaced, no PUFAs Paced, no PUFAs Paced, 3 wks PUFAs



Tissue samples from left atrial appendages stained for collagen. (A-C) Picrosirius-stained sections: cellular areas appear red and collagen-rich areas stain yellow. **(D-F)** MOVAT-stained sections: cellular areas appear red and fibrotic, collagen-rich areas stain light (yellow) colour.
Scale bar = 200 µm (4X objective), and 50 µm (20X objective).

Prevention of fibrosis, which is evident histologically (Figure 5), indirectly prevents conduction slowing and fragmented conduction; these results are key progenitors of the electrophysiological disturbances that lead to reentry and a propensity to AF.

Recent experiments using gene chip microarrays have indicated that atrial mechanical stretch induces an increase in messenger ribonucleic acid (mRNA) for genes implicated in fibrosis, hypertrophy, apoptosis, and inflammation. These increases in mRNA are attenuated or prevented by PUFA administration.[50]

Conclusions

The seemingly contradictory evidence on the effects of Ω-3 PUFAs on CV health can be reconciled with the hypothesis that they primarily act by preventing the consequences of tissue injury, especially stretch. This is an effect possibly more important than anti-inflammatory effects and unrelated to direct antiarrhythmic effects. These potential effects of Ω-3 PUFAs are consistent with the small, but definite effect on preventing death and heart failure-related events in patients with chronic heart failure, as well as death in patients following MI; both conditions involve active ventricular remodeling. These benefits may take many years to manifest, and would be expected to be more profound if Ω-3 PUFAs were administered earlier in the course of the disease, particularly prior to the cardiac injury itself. These data also suggest that Ω-3 PUFAs are unlikely to be effective as traditional "antiarrhythmic agents," administered after CV disease is fully established, or where the disorder is primarily myocardial ischemic in nature (as in the DART-2 study), as opposed to involving myocardial scarring and ventricular remodeling.

Thus, it seems reasonable to consume a diet high in Ω-3 fatty acids, or consider Ω-3 PUFA supplementation if such a diet is impractical. This may apply particularly to individuals at high risk of developing structural heart disease in the future, or those in the early stages of disease development, especially heart failure or MI. The full story of PUFA effects on human health remains to be written.

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Abstract of Interest

Fish Oil, But Not Flaxseed Oil, Decreases Inflammation and Prevents Pressure Overload-Induced Cardiac Dysfunction

DUDA MK, O'SHEA KM, TINTINU A, XU W, KHAIRALLAH RJ, BARROWS BR, CHESS DJ, AZIMZADEH AM, HARRIS WS, SHAROV VG, SABBAH HN, STANLEY WC.

AIMS: Clinical studies suggest that intake of omega-3 polyunsaturated fatty acids (omega-3 PUFA) may lower the incidence of heart failure. Dietary supplementation with omega-3 PUFA exerts metabolic and anti-inflammatory effects that could prevent left ventricle (LV) pathology, however it is unclear if these effects occur at clinically relevant doses, and if there are differences between omega-3 PUFA from fish (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), and vegetable sources (alpha-linolenic acid [ALA]).

METHODS: We assessed the development of LV remodeling and pathology in rats subjected to aortic banding treated with omega-3 PUFA over a dose range that spanned the intake of humans taking omega-3 PUFA supplements. Rats were fed a standard chow or diets supplemented with EPA+DHA or ALA at 0.7%, 2.3% or 7% of energy intake.

RESULTS: Without supplementation aortic banding increased LV mass and end systolic and diastolic volumes. ALA supplementation had little effect on LV remodeling and dysfunction. In contrast, EPA+DHA dose-dependently increased EPA and DHA, and decreased arachidonic acid in cardiac membrane phospholipids, and prevented the increase in LV end diastolic and systolic volumes. EPA+DHA resulted in a dose-dependent increase in the anti-inflammatory adipokine adiponectin, and there was a strong correlation between prevention of LV chamber enlargement and plasma levels of adiponectin (r=-0.78). Supplementation with EPA+DHA had anti-aggregatory and anti-inflammatory effects as evidenced by decreases in urinary thromboxane B(2) and serum TNF-alpha.

CONCLUSIONS: Dietary supplementation with omega-3 PUFA derived from fish, but not from vegetable sources, increased plasma adiponectin, suppressed inflammation and prevented cardiac remodeling and dysfunction under pressure overload conditions.

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