Heart Rate is Associated with Red Blood Cell Fatty Acid Concentration: the GOCADAN Study

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Abstract

Background—Consumption of omega-3 fatty acids (FAs) is associated with a reduction in deaths from coronary heart disease, arrhythmia, and sudden death. Although these FAs were originally thought to be anti-atherosclerotic, recent evidence suggests that their benefits are related to reducing risk for ventricular arrhythmia, and that this may be mediated by a slowed heart rate (HR).

Methods—The study was conducted in Alaskan Eskimos participating in the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) Study, a population experiencing a dietary shift from unsaturated to saturated fats. We compared HR with red blood cell (RBC) FA content in 316 men and 391 women ages 35–74 years.

Results—Multivariate linear regression analyses of individual FAs with HR as the dependent variable and specific FAs as covariates revealed negative associations between HR and docosahexaenoic acid (DHA; 22:6n-3; p= 0.004) and eicosapentaenoic acid (EPA; 20:5n-3; p=0.009) and positive associations between HR and palmitoleic acid (16:1n-7; p=0.021), eicosenoic acid (20:1n9; p=0.007), and dihomo-gamma-linolenic acid (DGLA; 20:3n-6; p=0.021). Factor analysis revealed that the omega-3 FAs were negatively associated with HR (p=0.003), while a cluster of other, non-omega-3 unsaturated FAs (16:1, 20:1, and 20:3) was positively associated.

Conclusions—Marine omega 3 FAs are associated with lower HR, whereas palmitoleic and DGLA, previously identified as associated with saturated FA consumption and directly related to cardiovascular mortality, are associated with higher HR. These relations may at least partially explain the relations between omega-3 FAs, ventricular arrhythmia, and sudden death.

RESULTS

Participant Characteristics

On average, the population was overweight (mean BMI = 27.8), had relatively low prevalence of diabetes (6.0%), low low-density lipoprotein cholesterol (LDL-C) (123 mg/dL) and triglycerides (116 mg/dL), and high high-density lipoprotein cholesterol (HDL-C) (60 mg/dL) (Table I). Smoking prevalence (59%) was almost three times that of the general U.S. population. Carotid plaque, defined as present or absent, was detected in approximately half of the participants.[7] Beta-blockers and heart-rate slowing calcium channel blockers were taken by 56 (8%) and 13 (2%), respectively, of participants.

HR

In univariate analyses, HR was higher in women than men (74±11 vs. 71±13 bpm, p=0.003), in current smokers vs. former/never smokers (74±12 vs. 71±11 bpm, p=0.023), was correlated negatively with body height (r= 0.164, p<0.001) and positively with percent body fat as measured by bioelectric impedance (r=0.075, p=0.046) and diastolic BP (r=0.120, p=0.001). In parallel analyses, HR showed modest positive associations with BMI (r=0.075, p=0.046) and waist/hip ratio (r=0.097, p=0.011). No correlations were observed between HR and age, body weight, systolic BP, or measures of physical activity as assessed by METS.

Individual FAs and HR

In multiple linear regression analyses of individual -3 FAs that considered gender, height, BMI, diastolic BP, current smoking, and heart-rate slowing medications as covariates, docosahexaenoic acid (DHA; 22:6n-3) was associated with lower HR (-0.60 bpm per % of

combination of omega-3 FAs had a significant negative relationship with HR. Although factor 1 included three non-omega-3 FAs, the main contribution was made by the omega-3 FAs.

Relation of Dietary and RBC Omega-3 FAs

A highly significant relation was observed between RBC membrane -3 FA relative concentrations and dietary -3 FA intake (partial correlation between factor 1 and total dietary omega 3=0.39, $p<0.001$ adjusted for sex, age, BMI, and smoking). However, the reported dietary -3 FA intake explained less than 16% of the total variation of -3 FAs found in the RBC membrane.

DISCUSSION

A recent report from the GOCADAN study found no association between fish oil consumption and prevention of arterial plaque,[7] suggesting that the lower cardiovascular death rate associated with higher omega-3 fatty acid intake in epidemiologic studies and treatment trials may not be related to slowed growth of arterial plaque but to other, as yet poorly understood, effects of fish oil. Studies have shown that fish oil consumption is negatively associated with sudden death and arrhythmia,[3,4,5,6] events which are themselves associated with a higher HR.[3,4] Consequently, reports of a negative association between fish oil consumption and HR[20,21,22,23] have led to the hypothesis that the fish oil effect on HR (as well as on HR variability)[9,23,24] may contribute to the lower death rate seen with higher fish oil consumption.

In this study, we have extended understanding of this topic by examining the associations between HR and RBC membrane content of FAs in a genetically and culturally homogeneous population of Eskimos, a group which has shifted from a traditional diet rich in fish oils and monounsaturated FAs to store-bought foods rich in saturated FAs and sugar.[11,12,19] The genetic homogeneity allows for a clearer evaluation of the effects of dietary changes on pathology than is typically possible in cross-sectional studies. This article reports for the first time that not only are the RBC levels of DHA and EPA negatively associated with HR, but also that the RBC content of several saturated FAs have positive associations with HR.

Fish Oil and HR

The data show a significant negative association between HR and a biomarker of omega-3 FA intake, RBC EPA and DHA levels. The average consumption of fish oil -3 FAs in this population is about 2.9 g/d compared with 0.2 g/d in the general U.S. population.[7,12] These results agree with other large cross-sectional studies linking fish intake with HR (Mozaffarian et al.[22] [n=5,096]; Chrysohoou et al.[23] [n=3,042]; Dallongeville et al.[25] [n=9,758]) and with intervention studies that show a negative association between fish oil and HR.[25,26,27] In some studies, the relations were stronger for DHA than for EPA,[25,28] and the effects of fish oil supplementation ranged from 2 to 5.8 beats/minute.

The mechanism responsible for the inverse relation between HR and -3 FAs (whether by biomarker or intake) is not known. It does not appear to require vagal innervation,[29] but in subjects with normal vagal tone, enhanced parasympathetic activity may play a role. Although Mori et al. reported that supplemental DHA lowered HR while EPA did not, we found a significant association between both long chain -3 FAs and HR in this population. Although there is evidence that EPA may not be incorporated into the cardiac phospholipids,[30] the current data suggest that the mechanism by which -3 FAs affect HR are mediated via the incorporation of these FAs into the heart muscle itself. One hypothesis emerging from these data is that the association between fish oil and HR results indirectly from greater cardiac efficiency, produced by the lower diastolic BP associated with fish oil -3 FAs, which may contribute to a slower

heartbeat. Our data show for the first time in an epidemiological study a significant association between diastolic BP and DHA ($p<0.001$).

The lower diastolic BP associated with fish consumption[28] is thought to result from fish oil stimulation of nitric oxide production, which increases vasodilatation of the large arterial vessels.[15] The exact mechanism is not known, but the evidence suggests that it may involve the inhibition of thromboxane-mediated vasoconstriction. The evidence further suggests that fish oils increase the left ventricular ejection fraction by enhancing ventricular filling during diastole, thus providing an energy-sparing promotion of diastolic relaxation.[31] Fish oils also raise the electrical threshold at which ventricular fibrillation can be induced and are effective in decreasing pro-arrhythmic thromboxane.[31] Other effects of fish oil consumption include improved blood flow[29] and decreased arterial stiffness.[32]

Diastolic BP, which is low in Eskimos, is negatively associated with increased fish oil consumption in both the Alaska Siberia Project (ASP) and the GOCADAN study.[13]

associated with other CVD risk factors. Palmitoleic acid (16:1n-7) and DGLA (20:3n-6) have been positively related to cardiovascular mortality, suggesting an association between cardiovascular mortality and HR that is affected by FAs.

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Table I

Baseline Characteristics

Variable	Mean±SD or N (%)	Range
Age (years)	50±10	35 – 74
Gender (women/men)	391/316	- - - - -
Heart rate (beats/minute)	73±12	46 – 122
Systolic blood pressure (mm Hg)	120±15	84 – 174
Diastolic blood pressure (mm Hg)	77±9	50 – 114
Hypertension (JNC-7, %)	203 (29%)	- - - - - -
Body mass index (kg/m^2)	27.8±5.9	16.7 – 54.9
Diabetes	44 (6%)	- - - - - -
Smoking (%)	415 (59%)	- - - - - -
Docosahexaenoic acid (% of total FAs)	6.7±2.2	0.6 – 13.7
Eicosapentaenoic acid (% of total FAs)	2.2±1.7	0.2 – 10.2
Palmitic acid (% of total FAs)	20.9±1.8	17.8 – 35.9
Palmitoleic acid (% of total FAs)	0.8±0.5	0 – 3
Eicosenoic acid (% of total FAs)	0.20±0.07	0.05 – 0.96
Dihomo-gamma-linolenic acid (% of total FAs)	1.7±0.5	0.4 – 3.6

Table III

Red blood cell fatty acid concentrations and factor loadings for varimax orthogonal five-factor solution after Kaiser normalization.

Fatty Acid	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Commonality
22:6n3	**−0.845**	0.216	0.061	0.145	0.157	0.810
20:5n3	**−0.819**	0.302	0.062	0.072	0.222	0.819
20:1n9	**0.806**	0.046	0.033	0.323	0.094	0.765
22:5n3	**−0.716**	0.044	0.057	0.379	0.324	0.767
20:3n6	**0.651**	0.416	0.050	0.116	0.101	0.623
18:1	**0.532**	**−0.569**	0.117	0.327	0.377	0.869
20:4n6	0.013	**0.934**	0.045	0.046	0.023	0.877
22:4n6	0.389	**0.837**	0.012	0.072	0.169	0.885
22:5n6	0.402	**0.767**	0.215	0.052	0.061	0.803
24:1n9	0.074	0.035	**0.976**	0.004	0.073	0.964
24:0	0.015	0.133	**0.966**	0.062	0.005	0.956
16:1	0.081	0.317	0.046	**0.852**	0.161	0.861
18:3n6	0.231	0.118	0.024	**0.809**	0.300	0.812
18:2n6	0.292	0.123	0.096	0.091	**−0.898**	0.924