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The Effect of Omega-3 Fatty Acids on Heart Rate Variability in Depressed Patients With Coronary Heart Disease

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Abstract

Objective—Low intake of omega-3 fatty acids (FAs) is associated with depression and with low heart rate variability (HRV), and all three are associated with an increased risk of death in patients with coronary heart disease (CHD). The purpose of this study was to determine whether omega-3 FA increases the natural log of Very Low Frequency (lnVLF) power, an index of HRV, and reduces 24 hour heart rate (HR) in depressed patients with CHD.

Methods—Thirty-six depressed patients with CHD randomized to receive 50 mgs of sertraline and two grams of omega-3/day, and 36 randomized to sertraline and a placebo, had 24 hour HRV measured at baseline and following 10 weeks of treatment.

Results—There was a significant treatment X time interaction for covariate adjusted lnVLF ($p=0.009$), for mean 24 hour HR ($p=0.03$), and for one minute resting HR ($p=0.02$). The interaction was not significant for three other measures of HRV. LnVLF did not change over time in the omega-3 arm, but decreased in the placebo arm ($p=0.002$), suggesting that omega-3 may have prevented or slowed deterioration in cardiac autonomic function.

Conclusions—The effects of omega-3 FAs on lnVLF and HR, although modest, were detected after only ten weeks of treatment with two grams per day of omega-3. Whether a longer course of treatment or a higher dose of omega-3 would further decrease HR, improve other indices of HRV, or reduce mortality in depressed CHD patients, should be investigated.

Keywords

depression; omega-3; heart rate variability

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Depression is a risk factor for death in patients with coronary heart disease (CHD).(1-3) Low dietary intake and low serum or red blood cell levels of two omega-3 fatty acids (FAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are associated with depression in patients with (4-6) and without (7-10) CHD. Low levels of these FAs also increase the risk for cardiac mortality, especially sudden cardiac death.(11-12) The connection between low omega-3 FA levels and both depression and cardiac death may be related to the role of omega-3 FAs in the nervous system. Omega-3 FAs are found at synapses throughout the human brain and are essential for neuronal functioning.(11-13-14)

The autonomic nervous system plays a key role in modulating heart rate (HR) and rhythm. Variability in HR reflects cardiac autonomic nervous system activity, with low HR variability (HRV) signifying excessive sympathetic and/or inadequate parasympathetic modulation of HR.(15) Low HRV has been reported in patients with depression (16-23) and in those with low blood levels of omega-3 FAs.(24-26) Low HRV is also a strong predictor of mortality in patients with CHD (27-29) and very low frequency power (VLF), a frequency domain measure of HRV that strongly predicts cardiac mortality, has been shown to account for up to 30% of the effect of depression on mortality following myocardial infarction.(30) There is some evidence that omega-3 FAs may improve HRV in patients with CHD, suggesting that it may also improve survival in these patients (24).

We recently conducted a double blinded, placebo-controlled trial in depressed patients with CHD to determine whether omega-3 FAs augment the efficacy of sertraline. The trial failed to support the study hypothesis; the depression outcomes did not differ between the omega-3 and placebo groups.(31) The purpose of this ancillary study was to test the hypothesis that omega-3 FA improves HRV in these patients.

Methods

The clinical trial methods and results have been reported elsewhere.(31) In brief, patients with documented CHD were recruited between May, 2005 and December, 2008 from cardiology practices in St. Louis, and from cardiac diagnostic laboratories affiliated with Washington University School of Medicine. Patients were excluded if they 1) had cognitive impairment, a severe comorbid psychiatric disorder, a high risk of suicide, or current substance abuse; 2) had an acute coronary syndrome (ACS) within the previous two months, a left ventricular ejection fraction (LVEF) <30%, advanced malignancy, or physical inability to participate; 3) were taking an antidepressant, anticonvulsant, lithium, or omega-3 supplements; 4) had a known sensitivity to sertraline or omega-3; or 5) refused to participate or were disqualified by their personal physician from participating in the study. Those who met the DSM-IV criteria for a current major depressive episode based on a structured depression interview (32), who scored ≥ 16 on the Beck Depression Inventory II (BDI-II) (33), and who met none of the exclusion criteria, were enrolled in the trial. The study was approved by the Human Research Protection Office at Washington University.

After a two week run-in phase, patients who continued to meet the BDI-II and DSM-IV depression criteria and who were not excluded for other reasons were scheduled for a laboratory visit. After resting supine on an examination table for 15 minutes, one minute resting HR and resting blood pressure were measured. Patients were then fitted with an ambulatory ECG monitor for a 24 hour recording. Following baseline assessments they were randomized to receive 50 mg of sertraline per day (Zoloft, Pfizer, Inc) plus either two capsules per day of omega-3 acid ethyl esters (930 mg of EPA and 750 mg of DHA; Lovaza, GlaxoSmithKline, Philadelphia, PA) or two corn oil placebo capsules, for 10 weeks. Compliance with both the sertraline and the omega-3 or placebo capsules was checked weekly by pill count, and by asking the participant to confirm that all pills that had been removed were actually taken as prescribed.

At baseline and 10 weeks, 40 ml of blood was drawn. Red blood cell (RBC) membrane EPA +DHA was assessed pre- and post-treatment by capillary gas chromatography and expressed as a percentage of the total RBC FAs.(34) Participants were also given a list of types of fish high in EPA and DHA omega-3 each week of the trial and asked how many servings of each they had consumed during the previous week.

Heart Rate Variability Analysis

The Holter ECG recordings were scanned at the HRV Core Laboratory at Washington University using a Cardioscan Holter scanner (Version 52a, DMS Holter, Stateside, NV) and analyzed with MARS Holter scanning software (Version 7.01, GE Medical Systems, Milwaukee, WI). The labeled beat-to-beat file was exported to a Sun workstation (Sun Microsystems, Palo Alto, CA) for advanced HRV analysis.

VLF power (0.0033-0.04hz in ms^2) was chosen *a priori* as the index of HRV for this study, based on evidence that it partially mediates the effect of depression on survival.(30) VLF measures the strength of underlying oscillations in heart rate at frequencies between 20 seconds and 5 minutes and is influenced by both the parasympathetic nervous system and the renin-angiotensin system.(35) The methods used for spectral analysis of ambulatory ECG data have been described previously.(36) Briefly, the sequence of normal-to-normal intervals was re-sampled and filtered to generate a uniformly spaced time series. Missing or noisy segments were replaced by linear interpolation from the surrounding signal. The average normal-to-normal interval was subtracted from the time series and fast Fourier transformed to extract the frequency components underlying the cyclic activity in the time series. Measurement of VLF power was based on *en bloc* analysis of the entire 24-hour recording.(36)

In addition to HR and VLF, other frequency domain indices were also derived. Frequency domain HRV indices represent the amount of variance in the HR sequence that is found in a specified range of underlying frequencies. Frequency domain indices are derived through fast Fourier transformation and spectral analysis of the ECG data. They are grouped in predefined ranges, and also include ultra low frequency (ULF; <0.00033 HZ), low frequency (LF; 0.04-0.15 HZ), and high frequency (HF; 0.15-0.4 HZ).(15)

Statistical Analysis

Chi-square tests and one-way analysis of variance models were used to compare the groups on demographic, psychiatric, and medical characteristics. Difference scores were calculated by subtracting post treatment from pre treatment values. Spearman correlation coefficients were used to determine the relationship of HR and HRV to the omega 3 index (% of DHA and EPA FAs in RBC). Model assumptions were examined for each analysis, and diagnostics (influence, residual, and outlier analyses) were performed for each patient characteristic and outcome measure. HR and HRV were adjusted for age, sex, beta blocker use, diabetes, and current smoking, based on previous studies showing that HR and HRV are influenced by these variables.(15)

Mixed models with an unrestricted covariance structure were fitted to the HRV data. The outcomes were regressed on the following fixed effects: group (between-subjects), time (within-subjects), and the group $\times$ time interaction. Intra-individual variation was modeled with a random effect for patient. The significance of the group $\times$ time interaction was tested to determine whether change in HR and HRV differed between the groups over time. Group means and standard deviations are reported for each HRV measure along with the test statistic and corresponding p-value.

No major violations of model assumptions were found in any of the statistical analyses. All hypothesis tests were two-tailed with $p < 0.05$ denoting statistical significance. SAS[®] version 9.1 was used for all statistical analyses. SAS Proc Mixed was used for the mixed model analyses.

Results

Of the 122 patients enrolled in the clinical trial, resting HR was not recorded in 7 patients in the placebo arm and 7 patients in the omega-3 arm because they had an implantable defibrillator with a pacemaker. The same 14 patients did not undergo 24 hour ambulatory monitoring because of the pacemaker. Of the 108 who underwent 24 hour ECG monitoring at baseline, HRV could not be measured in 6 patients due to monitor equipment failures and in 14 patients due to frequent (>25%) ectopic beats or paroxysmal episodes of atrial fibrillation. Thus, 88 patients had measurable 24 hour HRV at baseline. At the 10 week recording, 6 monitors failed, 4 patients dropped out of the study, and HRV could not be calculated in 6 patients with usable recordings at baseline due to >25% missing or noisy segments, atrial fibrillation, or atrial flutter. Thus, both baseline and 10 week (post-treatment) 24 hour ECG recordings were available for 72 patients: 36 in the placebo and 36 in the omega-3 group. The demographic and medical characteristics of the 72 patients with complete 24 hour ECG data were compared to those of the 50 who were excluded from 24 hour analysis due to missing data. The 50 excluded patients were less likely to have finished high school (54% vs. 71%) ($p = 0.03$) and more likely to have heart failure (54% vs. 31%) ($p = 0.04$) than the patients who were included in the analyses. There were no other demographic or medical differences.

Table 1 compares the demographic and medical characteristics of the patients in the omega-3 and placebo arms with 24 hour ECG. There were no differences in any of the variables, including the proportion of patients taking each class of major cardiac medications. There were only two changes in prescribed medications and no changes in dosages during the 10-week interval between the baseline and post-treatment recordings. One patient in the omega-3 arm was taken off of an ACE inhibitor and another was prescribed a statin.

Table 2 displays the data regarding depression, treatment adherence, and omega-3 index at baseline and after 10 weeks of treatment. Consistent with the primary results of the clinical trial, there were no between-group differences in BDI-II scores at baseline ($p = 0.44$) or after ten weeks of treatment ($p = 0.37$) (Table 2). There were high rates of adherence to both medications in both groups ($\geq 97\%$), and no difference between groups in the percentage of sertraline ($p = 0.55$), placebo, or omega-3 pills taken during the study ($p = 0.36$). Baseline RBC levels of DHA and EPA fatty acids were very similar for the groups at baseline ($p = 0.65$). After ten weeks, the level remained unchanged in the placebo group, but it was significantly higher in those who received omega-3 ($7.5\% \pm 1.8$) ($p < 0.0001$) (Table 2). The magnitude of change in the omega-3 index for the omega-3 group after 10 weeks was within the expected range for the formulation and dosage used in this study.(34)

Table 3 displays the adjusted 24 hour mean HRV and HR at baseline and after ten weeks. The HRV distributions were skewed and consequently the values were natural log transformed (ln). There was a significant treatment X time interaction for the primary measure of HRV, ln VLF ($p = 0.009$), and for HR ($p = 0.03$). However, the interactions for the secondary HRV indices were not significant [ln HF ($p = 0.12$), ln LF ($p = 0.11$), ln ULF ($p = 0.23$)]. Ln VLF remained unchanged in the omega-3 arm ($p = 0.92$), but decreased in the placebo arm ($p = 0.0002$). Although not statistically significant, trends toward similar changes in the other indices are apparent. On the other hand, HR increased in the placebo arm ($p = 0.02$) and decreased nonsignificantly in the omega-3 arm ($p = 0.41$). Effect sizes for HR and the HRV indices range from .29 to .65 (Cohen's D) and are reported in Table 3.

Table 3 also displays the mean baseline and post-treatment resting HR for the 72 patients included in the 24 hour HR and HRV analyses, and for the additional 36 patients (total n=108) who did not have usable 24 hour ECG data but who did not have a pacemaker and were in normal sinus rhythm at the time of the resting HR assessment. The results of both analyses parallel those of the 24 hour HR analysis.

The baseline omega-3 index was significantly correlated with both baseline HR ($r = -.33$; $p = 0.005$) and $\ln$ VLF ($r = .26$; $p = 0.03$) for the total sample. Change in the omega-3 index also correlated significantly with change in HR ($r = -0.29$; $p = 0.01$) and in $\ln$ VLF ($r = .32$; $p = 0.007$) after ten weeks of either omega-3 or placebo.

In order to determine whether initial depression severity or change in depression over time may have moderated the effects of omega-3 on HR or HRV, additional post hoc analyses were conducted. There was no evidence that either initial depression severity (VLF: $F_{1,68} = .01$; $p = .94$; HR: $F_{1,68} = .05$; $p = .82$) or pre-post change in depression (VLF: $F_{1,68} = 2.50$; $p = .12$; HR: $F_{1,68} = .15$; $p = .70$) moderated the relationship between omega-3 and change in either HR or HRV.

Discussion

Patients who received 2 grams per day of omega-3 FAs (930 mg of EPA and 750 mg of DHA) for 10 weeks maintained a stable level of $\ln$ VLF and showed a decrease in average 24 hour HR, whereas patients who received corn oil placebo capsules showed a decrease in $\ln$ VLF and an increase in HR. This effect was not moderated by baseline depression severity or by change in depression. There were no significant effects on the three other measures of HRV. That $\ln$ VLF did not change over time in the omega-3 arm, but decreased in the placebo arm, suggests that omega-3 may slow or prevent deterioration in cardiac autonomic function in patients with depression and CHD.

This is the first report demonstrating that omega-3 supplementation may prevent deterioration in HRV in cardiovascular populations, or at least those with depression. However, there is evidence that omega-3 supplementation prevents reductions in HRV associated with exposure to airborne particulate matter in elderly nursing home residents.(37) Although two grams of omega-3 per day had only a small effect on the evolution of HRV, it was detected after only ten weeks of treatment. Whether longer treatment or higher doses of omega-3 would further decrease HR or increase HRV is unknown.

The analyses were adjusted for beta blocker use, as well as for current smoking, diabetes, age and gender, because these factors are known to affect HR and HRV. However, about 80% of patients in both groups were taking beta blockers, which made it difficult to adequately adjust for their effects. As beta blockers would be expected to reduce HR and increase HRV, it is possible that the drug made it more difficult to detect an effect for omega-3 on HR and HRV.

As patients in both arms received sertraline, it is possible that the combination of sertraline plus omega-3 FA, and not omega-3 FA alone, prevented HRV from decreasing over time. However, it is also possible that sertraline contributed to the decrease in HRV, and that concurrent administration of omega-3 FA prevented this decline. Few studies have evaluated the effect of antidepressants on HRV, and they have produced conflicting results. Most had very small sample sizes ($Ns=6-24$), and HRV was calculated using widely different methodologies and measurement durations.(38) A recent review and meta-analysis of this literature, however, found that SSRIs, such as sertraline, have no significant effect on HRV. (39)

In one of the largest studies of the effect of antidepressants on 24 hour HRV in depressed CHD patients, Glassman and his colleagues found a decrease for six out of eight measures of HRV in 258 patients with a recent acute coronary syndrome after 16 weeks of treatment with either sertraline or placebo.(40) The drop was significant for ULF in patients given placebo and for LF in patients given sertraline. VLF declined 8% in patients receiving sertraline and 5% in those receiving placebo, but neither decline was statistically significant. Thus, it seems unlikely that sertraline produced a decline in HRV. It is more likely that depression and/or heart disease led to a decline in HRV in both studies, and that in our study, omega-3 FA prevented this decline.

As a result of paroxysmal episodes of atrial fibrillation or excessive ectopy, pacemakers, patient unwillingness, and mechanical or battery failure, only 72 of the 122 patients recruited for the study had 24 ambulatory ECG data at both baseline and follow-up that was suitable for calculating 24 hour HRV. However, only the patients who had a pacemaker were excluded from one minute resting HR measurement. Thus, resting HR was compared in 54 participants in the placebo arm, and in 54 in the omega-3 arm. The results were very similar to those of the 24 hour HR, with a significant treatment X time interaction ($p = 0.02$). Resting HR increased a mean of 2.5 bpm in the placebo arm ($p=0.03$), and decreased a mean of 1.6 bpm in the omega-3 arm ($p= 0.19$).

The mean baseline level of ln VLF was higher in the placebo than in the omega-3 arm. Although the difference was not significant, it is possible that regression to the mean at least partially accounts for the significant treatment X time interaction. However, there was also a significant treatment X time interaction for both 24 hour and resting HR, and HR did not differ between the groups at baseline but increased in the placebo arm and decreased nonsignificantly in the omega-3 arm at ten weeks.

Omega-3 FAs derived from food or dietary supplements have been shown to have beneficial effects on cardiovascular mortality.(41) Meta-analyses of up to 11 randomized controlled trials of omega-3 vs. placebo, with an aggregated sample of nearly 8,000 participants randomized to the intervention arms, found risk ratios of 0.7 (95% CI: 0.6-0.8) for fatal MI and 0.7 (95% CI: 0.6-0.9) for sudden cardiac death.(42)

Previous studies have provided evidence that omega-3 supplements may decrease HR in patients with CHD. In a systematic review of the literature, Mozaffarian and colleagues identified 30 articles meeting their inclusion criteria.(43) They found that omega-3 reduced HR an average of 2.5 bpm in trials with baseline HR ≥ 69 bpm, but had little effect in patients with lower baseline HR. Moreover, HR was reduced by a mean of 2.5 bpm in trials lasting >12 weeks, but there was no significant effect on HR in briefer trials. Interestingly, there was no relationship between reduction in HR and the dosage of omega-3 (range: 0.81 – 15 grams/day), age, population, methods of HR measurement, or study design.

O'Keefe et al conducted the trial that used the lowest dose of omega-3, and yet produced a 5 bpm reduction in resting heart rate and shorter HR recovery after exercise in a group of post-MI patients.(44) However, these patients received 810 mg/day of EPA/DHA for four months. The present study lasted only 10 weeks, so it is possible that the difference in HR between groups would have increased if the trial had been longer.

There is less evidence that omega-3 improves HRV. O'Keefe and colleagues found a significant reduction in HR as reported above, but only one index of HRV, high frequency power (HF), increased significantly.(44) Christensen and colleagues found that the 24 hour time domain HRV index SDNN, the standard deviation of N-N intervals, improved in a group of post-MI patients with poor ventricular function (LVEF <40) after receiving 4.3 g/day of EPA/DHA.

(24) SDNN was the only index of HRV reported in that study, but it has been found to predict mortality following MI.(45)

Studies of HR, HRV, and depression following acute MI, and most studies of HR and HRV in medically stable CHD patients, have found HRV to be lower and HR higher in depressed than in nondepressed patients.(46) In an attempt to determine whether low HRV accounts for the effect of depression on mortality, a statistical mediation model was applied to data collected in a follow-up study of 311 depressed and 367 nondepressed patients with a recent acute MI. (30) Ln VLF was selected as the index of HRV, as it was in the present study, because of its prognostic importance in post-MI patients. Ln VLF was significantly lower in the depressed patients. During a median follow-up of 24 months, the depressed patients were at higher risk for all-cause mortality, even after adjusting for potential confounders (HR = 2.8; 95% CI: 1.4 to 5.4, $p < .003$). When Ln VLF was entered into the model, the hazard ratio for depression dropped to 2.1 (95% CI: 1.1 to 4.2, $p = 0.03$), indicating that Ln VLF accounted for about 30% of the total mortality risk. The results of the study suggested that low VLF at least partially mediates the effect of depression on survival after acute MI.

How omega-3 improves HRV and reduces the risks of arrhythmia and sudden cardiac death is not known, but omega-3 is known to inhibit fast voltage-gated sodium channels (47) and L type calcium channels.(48) Even small doses of EPA and DHA have been found to lower plasma NE concentrations in normal volunteers (49) and in hypertensive patients (50), although some studies have not found this effect.(51- 52) These mechanistic studies vary considerably in the types and amounts of omega-3 FAs that were tested, as well as in the populations that were studied and in the study designs. More work is needed to understand the pathways through which either EPA and/or DHA may reduce HR and improve or inhibit further decline of HRV, and reduce risk of arrhythmias and SCD.

In conclusion, a low dietary or RBC level of omega-3FAs is associated with depression, low HRV, and sudden cardiac death in patients with CHD. Patients with major depression and CHD may experience an accelerated decline in cardiac autonomic function, and this may explain why they are at greater risk for mortality than are nondepressed patients with CHD, even years after the event occurred. The present study found that a 10-week course of 2 grams per day of omega-3 (EPA and DHA) prevented or at least slowed this decline. Future studies should extend the treatment period to determine whether omega-3 may actually increase HRV and further reduce HR in this high risk group of patients with CHD. Additional future studies should examine whether this effect is also seen in other populations, as only depressed CHD patients were included in this study.

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List of acronyms

CHD	coronary heart disease
FAs	fatty acids

EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
HRV	heart rate variability
VLF	very low frequency
ACS	acute coronary syndrome
LVEF	left ventricular ejection fraction
BDI –II	Beck Depression Inventory
RBC	red blood cell
HR	heart rate
ULF	ultra low frequency
ECG	electrocardiogram
ACE	angiotensin converting enzyme
BPM	beats per minute
MI	myocardial infarction
SDNN	standard deviation N-N

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Table 1

Baseline Demographic and Medical Characteristics

Characteristic	Group Assignment		P-value
	Placebo (n=36)	Omega3 (n=36)	
Age (years)	57.9 ± 8.5	56.8 ± 10.0	0.61
Gender (Female)	11 (30.6%)	17 (47.2%)	.015
Caucasian	31 (86.1%)	29 (80.6%)	0.53
Education > 12 years	28 (77.8%)	23 (63.9%)	0.19
BMI (kg/m ²)	32.8 ± 7.3	34.4 ± 8.5	0.39
Cigarette Smoker (current)	5 (13.9%)	10 (27.8%)	0.15
Hypertension	29 (80.6%)	29 (80.6%)	1.00
Diabetes	13 (36.1%)	12 (33.3%)	0.80
History of acute coronary syndrome	21 (58.3%)	20 (55.6%)	0.81
History of coronary bypass surgery	13 (36.1%)	10 (27.8%)	0.45
History of percutaneous intervention	25 (69.4%)	22 (61.1%)	0.46
New York Heart Association (NYHA) Classification			0.38
No heart failure	26 (72%)	24 (67%)	
NYHA class 1-2	10 (28%)	8 (22%)	
NYHAC class 3	0 (0%)	4 (11%)	
Depression			
History of depression	23 (65.7%)	21 (61.8%)	0.73
Duration of current depressive episode (months)	16.8 ± 22.5	11.8 ± 16.0	0.28
History of depression treatment	21 (58.3%)	22 (61.1%)	0.81
Medication Use			
Aspirin	33 (91.7%)	28 (77.8%)	0.10
Calcium channel blocker	8 (22.2%)	14 (38.9%)	0.12
Beta blocker	30 (83.3%)	28 (77.8%)	0.55
ACE inhibitor	16 (44.4%)	16 (44.4%)	1.00
Statin	29 (80.6%)	27 (75.0%)	0.57

Continuous variables are reported as means ± standard deviations; categorical variables are listed as number (percentage of subjects with the characteristic). Chi-square or Fisher's exact tests and analyses of variance were used to determine significance.

Table 2

Depression, Percent Omega-3 RBC, and Treatment Compliance

Characteristic	Group Assignment		P-value
	Placebo (n=36)	Omega3 (n=36)	
Beck Depression Inventory II score			
Baseline	29.5 ± 10.2	27.9 ± 7.8	0.44
Post-treatment	15.9 ± 10.6	13.0 ± 8.1	0.37
Omega-3 index (% EPA + DHA in RBC)*			
Baseline	4.8 ± 1.4	4.6 ± 1.6	0.65
Post-treatment	4.7 ± 1.3	7.5 ± 1.8	<0.0001
Cumulative treatment adherence (% days pill removed)			
Omega-3 or corn oil placebo capsules	97.8 ± 2.6	96.9 ± 5.1	0.36
Sertraline	99.1 ± 1.7	98.8 ± 2.4	0.55
Fish consumption (mean servings per week)	.8 ± 1.1	.7 ± 1.3	0.78

Data are reported as means ± standard deviations; analysis of variance was used to determine significance.

* EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; RBC = red blood cells

Table 3
Adjusted Mean Baseline, Post Treatment 24 Hour HRV, HR, and resting HR by Treatment Group¹

Indices ²	Placebo		Omega-3		Treatment × Time Interaction (pre-post change) Test Statistic, F _{1, 70} P Cohen's D ³		
	Baseline (n=36)	Post Treatment (10 weeks) (n=36)	P	Baseline (n=36)		Post Treatment (10 weeks) (n=36)	P
Primary							
Ln VLF	7.06 ± .83 (6.77, 7.34)	6.80 ± .91 (6.50, 7.10)	0.0002	6.67 ± .87 (6.39, 6.95)	6.67 ± .87 (6.37, 6.96)	0.92	F=7.32 p=0.009 D=.65
24 Hour HR (bpm)	71.7 ± 9.2 (67.8, 75.7)	74.9 ± 11.4 (71.1, 78.7)	0.02	73.4 ± 14.1 (69.5, 77.4)	72.3 ± 11.4 (68.5, 76.1)	0.41	F=5.10 p=0.03 D=.54
Secondary							
Ln HF	4.82 ± 1.06 (4.46, 5.18)	4.58 ± 1.08 (4.23, 4.93)	0.02	4.43 ± 1.10 (4.08, 4.79)	4.43 ± 1.04 (4.08, 4.78)	0.96	F=2.51 p=0.12 D=.38
Ln LF	5.89 ± 1.10 (5.52, 6.26)	5.75 ± 1.07 (5.40, 6.11)	0.09	5.48 ± 1.14 (5.11, 5.86)	5.53 ± 1.06 (5.17, 5.88)	0.60	F = 2.59 p = 0.11 D = .38
Ln ULF	9.08 ± .73 (8.84, 9.31)	8.97 ± .69 (8.73, 9.21)	0.24	9.00 ± .70 (8.76, 9.23)	9.04 ± .74 (8.80, 9.28)	0.60	F = 1.44 p= 0.23 D = .29
1 Minute Resting HR (bpm)	67.0 ± 11.1 (63.4, 70.7)	69.0 ± 11.7 (65.1, 72.9)	0.16	68.0 ± 11.0 (64.3, 71.7)	65.5 ± 11.7 (61.6, 69.5)	0.09	F=4.85 p = 0.03 D = .53
1 Minute Resting HR (bpm) (N=108) ⁴	66.5 ± 11.9 (63.3, 69.7)	69.0 ± 11.5 (65.9, 72.1)	0.03	67.8 ± 12.0 (64.6, 71.1)	66.2 ± 11.9 (62.9, 69.5)	0.19	F=5.96 p=0.02 D=.47

¹ HR and HRV data are reported as mean ± standard deviation (95% confidence intervals), and are adjusted for age, gender, smoking, diabetes, and beta blockers.

² All HRV indices are natural log-transformed.

³ Cohen's D is a function of the group sample size and the interaction F-value. Guide for interpretation of effect sizes: 0.2 (small), 0.5 (medium), 0.8 (large).

⁴ Includes all patients without a pacemaker and in sinus rhythm at measurement.