EDITORIAL COMMENT

Polyunsaturated Fatty Acids and the Post-Infarct Patient

A Recipe for Baroreflex Health?*

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Robust neural regulation of the heart and circulation is fundamental to cardiovascular health. Conversely, in the post-infarct population (1) and in patients with heart failure (with or without coronary artery disease) (2,3), impaired arterial baroreflex sensitivity (BRS) (i.e., a blunted reflex heart rate [HR] response to stimulation or unloading of arterial baroreceptors) and blunted heart rate variability (HRV) are 2 independent, primarily vagally mediated, markers of total cardiac mortality and sudden cardiac death (SCD). These events are attenuated by interventions such as beta-blockade and exercise-training, which augment vagal drive and diminish sympathetic tone. However, contemporary therapy does not eliminate SCD; some high-risk patients are intolerant or non-adherent to these prescriptions, and there are limitations to device therapy as a global health strategy. Thus, there remains a need for additional simple and inexpensive interventions to decrease the occurrence of SCD.

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Results of randomized trials involving post-infarct patients have stimulated interest in piscine omega-3 polyunsaturated fatty acids (n-3 PUFAs), primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), for this purpose. In the DART (Diet and Reinfarction Trial), men advised to supplement their diet with either 2 weekly servings of fatty fish or daily fish oil capsules experienced a 29% reduction in all-cause mortality and 32% fewer deaths from ischemic heart disease (4). In the GISSI (Gruppo Italiano per lo Studio della Sopralevvivenza nell’Infarto miocardico acuto-1) Prevenzione Trial, 11,324 patients were randomized to a daily supplement of either 1 g n-3 PUFAs, vitamin E, both, or neither. After 3.5 years, there were relative risk reductions of 45% in SCD and 20% in all-cause mortality in the n-3 PUFA group, with the former evident within 4 months of randomization (5).

Omega-3 polyunsaturated fatty acids might reduce vulnerability to ventricular arrhythmias after myocardial infarction by acting directly on myocyte sodium and calcium currents (6) or indirectly, by restoring vagal HR modulation. Christensen et al. (7) reported a dose-dependent increase in HRV in healthy men, but not in women, after 12 weeks of daily supplementation with either 2.0 g or 6.6 g n-3 PUFAs (7). Earlier, these authors had randomized 55 post-myocardial infarction patients with an ejection fraction <40% to 12 weeks of either 5.2 g/day of n-3 PUFAs or olive oil, and observed a significant increase in the standard deviation of R-R intervals in those allocated fish oil (8). O’Keefe et al. (9) allocated 18 men with an ejection fraction <40% after myocardial infarction either placebo or n-3 PUFA capsules (585 mg DHA and 225 mg EPA daily) for 4 months, and noted, after active therapy, a significant fall in HR and an increase in high-frequency (HF) HR spectral power but not low-frequency (LF) HR spectral power (which is primarily sympathetically mediated) (10).

If these markers of tonic vagal HR modulation are improved by n-3 PUFAs, it would be logical to assume that fish oils also augment reflex vagal HR modulation. In this issue of the Journal, Radaelli et al. (11) have tested the hypothesis that dietary n-3 PUFA supplementation enhances the arterial baroreflex control of both HR and blood pressure (BP). Post-myocardial infarction non-diabetic patients with ejection fractions <40% were randomly allocated 2 g/day of n-3 PUFAs (n = 15) or placebo (n = 10) capsules. After 4 months of n-3 PUFAs, reflex depressor and bradycardic responses to stimulation of carotid baroreceptors using graded-neck suction were augmented by 78% and 41%, respectively, and the alpha index of BRS (derived from cross-spectral analysis of BP and HR) increased by 36%; R-R interval variance increased by 50%, and HF-HRV power increased by 76%. A lack of BP effect suggested that these autonomic effects of PUFAs did not result from greater afferent stimulation of arterial baroreceptors by improved hemodynamics. The authors concluded that, in addition to increasing HRV in stable mild-to-moderate congestive heart failure, n-3 PUFA supplementation augments vagal and sympathetic efferent responsiveness to arterial baroreflex stimulation, and proposed that these actions might reduce the risk of SCD.

This carefully designed and executed study of post-infarct patients, already treated with angiotensin-converting enzyme inhibitors, beta-adrenoceptor antagonists, and statins, demonstrates an additional effect of n-3 PUFA supplementation on several independent yet complementary markers of autonomic circulatory control with known prognostic implications. These observations stimulate 4 questions.

Why do these findings contrast with prior observations in healthy subjects? In young healthy men, supplementation with 4 weeks of fish oil (0.81 g EPA/day) had no effect on reflex HR, forearm vasoconstrictor, or plasma norepinephrine responses to hypotensive (−40 mm Hg) lower body
negative pressure, a maneuver that unloads both carotid and aortic baroreceptors (12). More recently, Geelen et al. (13) randomized 84 healthy women and men, age 50 to 70 years, to 3 months of dietary supplementation with either fish (3.5 g/day) or sunflower oil. Each of the LF alpha indexes for BRS, the SD of R-R variability, and HF and LF HRV spectral power tended to decrease, rather than increase, in those receiving fish oil. Unclear is whether the discordance between the present observations and previous studies represent an action of n-3 PUFAs specific to the post-infarct population (and if so, why?), an effect specific to baroreceptor stimulation (11) as opposed to baroreceptor unloading (12), which elicits reflex sympathetic activation, or differences in baseline diet between these various populations.

Do these subjects reflect the heart failure population? Radaelli et al. (11) describe their patients as having stable mild-to-moderate congestive heart failure, yet only 52% were receiving diuretics. Thus, many would be considered post-infarct patients with asymptomatic ventricular systolic dysfunction. This consideration becomes important when interpreting frequency domain estimates of HRV, and in particular LF spectral power (10). Importantly, neither the BRS nor the HRV of subjects in the present study were depressed to values shown to increase the risk of SCD (1,14). Indeed, the mean alpha index reported in the present study is similar to that described by this group in healthy men >50 years of age (15).

Only 1 of the 25 subjects in the present study was female. Women, unlike men, may not respond to n-3 PUFA supplementation (7,9,13). Thus, the autonomic effects of n-3 PUFA in both men and women with chronic congestion, and in particular those at high risk because of severely depressed HRV or BRS, should be determined before the present findings are applied broadly to the chronic heart failure population.

Is the assumption of clinical benefit appropriate? Whether n-3 PUFAs are anti-arrhythmic in humans remains controversial. Subsequent to their original paper, the DART investigators reported a 29% increase in the risk of cardiac death and a 54% increase in the risk of SCD in men with angina advised to consume oily fish or fish oil capsules (16). Recent trials involving patients at highest risk (i.e., those with implanted cardioverter-defibrillators [ICD]) for either primary or secondary prevention of SCD suggested little or no benefit (17,18), and possibly harm (19). In those randomized to 1.8 g/day of n-3 PUFAs versus placebo, Raitt et al. (19) observed higher rates of ICD discharge elicited by ventricular tachycardia or fibrillation in patients with ventricular tachycardia as their qualifying entry rhythm.

Do the present observations suggest a hypothesis to account for these findings? In addition to augmenting tonic and reflex markers of vagal HR modulation, randomization to n-3 PUFAs resulted in a nearly 4-fold increase in LF HRV spectral power and more than doubling of the LF/HF ratio (11). The neural mechanisms responsible for these changes were not elucidated. To do so would require quantification of sympathetic outflow to the heart or to skeletal muscle (10). The authors take the position that their observations were derived from patients with chronic congestive heart failure, in whom, paradoxically, LF spectral power is inversely related to sympathetic discharge frequency (20), and therefore should be interpreted as sympatho-inhibitory (11). Conversely, if these observations were derived from healthy subjects, or from well-compensated, non-edematous patients with mild or moderate left ventricular systolic dysfunction (as appears to be the case for the present study), such changes may well reflect an increase in sympathetic nerve traffic (10,21,22). Because spectral analysis assesses vagal and cardiac sympathetic modulation of sino-atrial discharge within the HF and LF ranges, but not the intensity of nerve firing directed at the ventricles, the hypothesis that n-3 PUFAs might exert a pro-arrhythmic action in heart failure, by augmenting reflexively sympathetic outflow, cannot be dismissed without experiment. In their discussion, the authors acknowledge that they tested only the sympatho-inhibitory limb of the arterial baroreflex and therefore cannot exclude the possibility that PUFA supplementation might enhance sympatho-excitatory responses to baroreflex unloading. Radaelli et al. (11) should be congratulated for demonstrating that n-3 PUFAs can improve baroreflex health. We await with interest the results of the GISSI Trial (23) of n-3 PUFA supplementation in heart failure.

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