EDITORIAL COMMENTARY

More seafood to control heart rate?

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It is common knowledge that fish oils have several beneficial effects. The potential benefit of fish oils was first recognized in the 1970s when researchers found that North Western Greenland Eskimos who consumed large amounts of fat from seafood displayed little or no cardiovascular disease.1 Extensive research in the last three decades, recently reviewed,2 has confirmed the advantages of dietary intake of fish oils, particularly of the omega-3 polyunsaturated fatty acids (ω-3 PUFAs) contained in fish oils. Benefits have been demonstrated not only for healthy people but also for patients after myocardial infarction and for patients with atherosclerosis, atrial fibrillation, or heart failure. According to this view, ω-3 PUFAs not only are a simple nutritional supplement but are a tool to help in the prevention and treatment of cardiovascular disease.

Among the beneficial effects of dietary supplementation with fish oil is a lower resting heart rate. A meta-analysis of 30 clinical trials showed that a fish oil diet decreased heart rate by an average of 1.6 bpm, but limiting the analysis to trials with a higher baseline heart rate (≥69 bpm) or longer treatment (≥12 weeks) yielded a larger reduction of 2.5 bpm.3

It is well known that lowering the heart rate lowers the risk of cardiovascular death. A lower heart rate is beneficial for a variety of cardiac conditions and is a main therapeutic target in patients with ischemic heart disease and coronary artery disease. Mortality benefits associated with the use of beta blockers in patients with ischemic heart disease and heart failure are partly attributable to the rate-slowing action of these drugs.4,5 Importantly, the link between high resting heart rates and increased mortality is well established both in the general population and in specific populations with cardiovascular and other diseases.6 Therefore, the development of tools for pharmacologic/nutritional control of heart rate is of great interest.

In a study reported in this issue of Heart Rhythm, Verkerk et al7 identify the cellular mechanism responsible for the heart rate–slowing action of fish oil: inhibition of the funny current \( I_f \). By comparing cells isolated from fish oil–fed rabbits and control-fed rabbits, without acute delivery of fatty acids to cells through a perfusing solution during patch-clamp experiments, the authors determined that the effect is due to incorporation of fatty acids into the membranes of pacemaker cells.

The funny current has an established role in generating spontaneous activity of pacemaker cells and in mediating autonomic modulation of heart rate, achieved by controlling the steepness of diastolic depolarization.8,9 The concept of \( I_f \)-based pacemaking represents a basic cellular mechanism in cardiac physiology, but practical applications of this concept also have clinical relevance. For example, \( f \)-channels are the target of “pure heart rate–reducing” agents, a family of drugs able to slow heart rate without other cardiovascular side effects. Among these agents, ivabradine is the only member presently available on the market; it is prescribed as therapy for chronic stable angina.

The study by Verkerk et al uncovers yet another clinically relevant application of the concept of funny channel-based pacemaking, one associated with nutritional health. The study is important because it provides a cellular/molecular interpretation of one of the recognized beneficial effects of ω-3 PUFAs.

Their finding is provocative because it raises some intriguing questions. The first question is, to what extent does \( I_f \) down-regulation and related bradycardia contribute to the overall improvement of cardiac health associated with fish oil diets?

In discussing their data, the authors comment that the 31% cycle length prolongation observed in single cells from animals that were fed fish oil would require more than the 30% \( I_f \) down-regulation measured in the patch-clamp experiments. However, the argument that 31% cycle length prolongation requires almost complete block of \( I_f \) is based on evidence from studies in which rate changes were measured using Cs+, which is not a highly selective \( I_f \) blocker.10 It is of note that cycle length prolongation of approximately 30% in this study was obtained with ivabradine 3 μM,11 a concentration that exerts a maximal \( f \)-channel block of 56% in voltage-clamp conditions12 and likely more reduced block during activity.

Also in relation to data quantification, the authors argue that mechanisms other than \( I_f \) contribute to fish oil–induced

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slowing, as cycle length and diastolic depolarization rates still differed between fish oil cells and control cells in the presence of either Cs\(^+\) or zatebradine. However, again this comparison is based on the assumption of full I\(_f\) block, a condition not easily achieved because Cs\(^+\), beyond being unselective, blocks I\(_f\) only partially at diastolic voltages\(^{13}\) and because the action of zatebradine on I\(_f\) is use dependent, with block relief at negative voltages.\(^{14}\) This suggests that only a fraction of the current is blocked by zatebradine during activity when f-channels undergo repetitive cycling between open and closed states.\(^{12}\) Thus, although the data of Verkerk et al clearly indicate a contribution of mechanisms other than I\(_f\) to rate slowing (i.e., action potential prolongation), the effect on rate of I\(_f\) reduction by fish oil may, in fact, be somewhat more important than indicated.

As reported by Verkerk et al, the bradycardia induced by fish oil was 11% in perfused hearts and 24% in single cells. These effects are larger than those reported in humans (2%–4%). The authors explain these variations as being due to differences in I\(_f\) conductance density between rabbits and humans. In my opinion, physiologic reflex mechanisms that normally operate in vivo but are lacking in isolated hearts/cells also might contribute to these differences. Unfortunately the study by Verkerk et al does not include measurements of rate in free-moving living animals, which would allow a comparison with previously reported data from human studies. Of note, although the degree of heart rate reduction associated with fish oil diets in humans appears quite small, a 2.5-bpm decrease\(^{3}\) on a population-wide basis reduction associated with fish oil diets in humans appears compatible with decreased I\(_f\) availability and a slower rate if fish oil supplementation had the effect of stimulating the formation of caveolar lipid rafts. Indeed, f-channels have been shown to colocalize to caveolar-rich lipid rafts, and lipid-raft disruption by methyl-\(\beta\)-cyclodextrin–mediated cholesterol depletion has been shown to lead to increased I\(_f\) availability and rate acceleration.\(^{15}\) However, because lipid-raft disruption is associated with substantial changes in channel kinetics,\(^{17}\) the lack of evidence for fish oil–induced kinetic modifications in the study by Verkerk et al rules against this intriguing hypothesis. It will be interesting to determine which is the operating mechanism.

The work of Verkerk et al proposes a new investigational paradigm involving measurement of heart rate modifications potentially associated with nutritional factors and may impact future research on the cardiovascular action of dietary supplements interacting with funny channels and more generally with the cellular/molecular processes underlying control of cardiac rate.

**References**