A substantial body of evidence, including findings from experiments, observational studies, and clinical trials, indicates that consumption of fish or fish oil reduces the incidence of fatal ventricular arrhythmias, manifested as coronary death or sudden death (1). It is of growing interest whether fish or fish oil consumption might influence atrial arrhythmias, particularly atrial fibrillation (AF), which is the most common cardiac arrhythmia and afflicts more than 2.2 million Americans (2). The incidence of AF increases dramatically with age—lifetime risk after age 40 is 1 in 4—and results in fatigue, reduced exercise tolerance, and increased risk and severity of stroke (2). Once AF has developed, anticoagulation reduces stroke risk (although with attendant bleeding risks), but other treatment options are limited. Thus, prevention of AF should be the paramount goal.

Several strengths are evident. An experimental design generally minimizes confounding from other known or unknown risk factors. The dogs were otherwise healthy and fed reasonable doses of fish oil, providing a relatively unperturbed biologic model. Controlled vagal stimulation, electrophysiological induction of AF, and anesthesia limited the pathways influencing the risk of AF, allowing evaluation of a relatively direct (rather than indirect) effect of fish oil on the heart (e.g., it is unlikely that findings could be explained by effects of fish oil on autonomic tone, vascular resistance, or endothelial function). Myocardial biopsies provided direct confirmation of the effects of fish oil on atrial n-3 fatty acid content and connexin levels.

Limitations are also present. The fish oil treatments were neither randomized nor blinded, raising the possibility of bias due to differences in the experimental groups or in the investigators’ induction or ascertainment of AF. The intravenous substudy lacked an appropriate control group, as dogs with inducible AF in the first attempt were simply re-examined after an intravenous infusion (the less common occurrence of AF during the second attempt might have been seen in any group of dogs in whom AF was inducible in a first attempt, reflecting a type of regression toward the mean). More meticulous consideration of such issues in epidemiologic design would have enhanced the study. Also, of course, the generalizability of these findings to spontaneously occurring AF in humans is unclear.

Atrial fibrillation represents a final clinical manifestation of multiple and likely relatively distinct pathoetiologic influences, from adrenergic and vagal activity in athletes and younger adults to reduced myocardial compliance and ventricular dysfunction in older adults. This heterogeneity suggests that risk factors and effective treatments will likely vary depending on the specific characteristics and predominant pathoetiologies of AF in the population (e.g., comparing younger vs. older adults, spontaneous vs. postoperative AF, or primary prevention vs. restoration of sinus rhythm vs. prevention of recurrence). These issues must be carefully considered when weighing the generalizability and implications of different investigations, and this heterogeneity may account for the conflicting results of prior (and likely future) studies of fish or fish oil and AF.

In a prospective observational study among older adults, consumption of tuna or other broiled or baked fish was associated with a 35% lower incidence of AF (p = 0.001), after adjustment for other risk factors (4). In contrast, 2 subsequent observational studies did not find inverse associations between fish consumption and AF incidence (5,6). Conversely, in an open-label randomized trial among 160 patients undergoing cardiac surgery, perioperative fish oil treatment (2 g/day) reduced the occurrence of postoperative AF from 33.3% to 15.2% (p = 0.01) (7). The clinical heterogeneity of AF suggests that the major mechanisms for AF prevention by fish oil may vary in different populations. In the postoperative setting, mechanisms that produce
relatively acute benefits may predominate, such as possible effects of fish oil on postischemic recovery (8), left ventricular filling (9), vagal activity (10), or atrial electrophysiology (e.g., due to effects on myocardial ion channels [11] or connexins [3,12]). For the AF seen with aging, mechanisms that produce longer-term benefits may be more important, such as effects of fish oil on blood pressure (13), systemic vascular resistance (14,15) and reactivity (16,17), and endothelial activation (18), which might mitigate long-term ventricular (and atrial) remodeling and augment myocardial compliance.

Sarrazin et al. (3) have added an important new piece to this puzzle. In addition to demonstrating clear anti-AF effects of fish oil in a controlled experiment, the effects of fish oil consumption on connexin levels and the relations of these differences with inducibility of AF are particularly intriguing. In vitro, n-3 fatty acids affect connexins, improving the functional distribution of cell interface connexins in cultured rat astrocytes (19) and suppressing hypoxia-reperfusion-induced phosphorylation of connexin 43 in cultured human endothelial cells (12). The present findings confirm in vivo that fish oil consumption affects connexins and suggest a novel potential mechanism for the antiarrhythmic effects of n-3 fatty acids that should stimulate further research in this field. The positive results of the observational study (4) and open-label trial (7), together with the present findings from Sarrazin et al. (3), paint a tantalizing picture that a simple, low-risk, and low-cost dietary intervention could reduce the incidence of AF, the most common complication of cardiac surgery and the most common cardiac arrhythmia in the general population.

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