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Fish oil for atrial fibrillation prevention: Can we intervene soon enough to make a difference?

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The atria have dual physiologic roles, serving both to facilitate ventricular filling and acting as sensors for blood volume, releasing natriuretic peptides that promote renal sodium excretion when filling pressures are elevated. While the atria typically operate with low diastolic pressures, they adapt rapidly to increased pressures with the development of chamber thinning and dilatation. Dilatation is limited by fibroblast proliferation and extracellular matrix accumulation that increases atrial stiffness. Atrial structural remodeling in response to hemodynamic overload is characterized by matrix metalloprotease activation, fibroblast proliferation, and increased abundance of extracellular matrix components.¹

Atrial structural remodeling can constitute both a risk factor for the development of atrial fibrillation (AF) and a response to the presence of AF. In individuals with AF, atrial structural remodeling contributes to the transition from paroxysmal to persistent AF, as a result of increased tissue area for reentry, and of heterogeneous and slowed conduction. Heterogeneity, whether of conduction or repolarization, is critical for reentrant electrical activity. While electrical remodeling (altered refractory period) tends to predominate as the earliest response to atrial tachycardia, atrial structural remodeling is typically the earliest response to increased atrial pressures and cardiac hemodynamic overload. In recognition of the significance of atrial structural remodeling, investigators have sought to identify interventions that can help to minimize its occurrence.

In experimental animal models that increase atrial pressures (heart failure, myocardial infarction, hypertension, valvular dysfunction), several mechanistically distinct interventions have been shown to attenuate the development of atrial fibrosis. In a canine heart failure model induced by ventricular tachypacing, pretreatment with enalapril² (an angiotensin-converting enzyme inhibitor) or simvastatin³ attenuated but did not eliminate the development of atrial fibrosis. In a rat model of heart failure induced by myocardial infarction, increased left atrial fibrosis was attenuated by spironolactone (an aldosterone antagonist) but not by an angiotensin-converting enzyme inhibitor or beta-adrenergic receptor blocker.⁴ In a canine heart failure model due to ventricular tachypacing, pretreatment with omega-3 polyunsaturated fatty acids (ω 3-PUFAs) attenuated ventricular tachypacing-induced hemodynamic dysfunction and significantly decreased the development of atrial fibrosis, the heterogeneity of conduction, and the duration of induced AF episodes.⁵ Similarly, in a canine model of 2 weeks simultaneous atrial and ventricular pacing (SAVP), pretreatment with ω 3-PUFAs reduced the abundance of collagen in the atrial appendage, decreased matrix metalloprotease 9 activation, and decreased the inducibility of AF induced with an extrastimulus protocol.⁶ Pretreatment with ω 3-PUFA

appears to be an effective strategy for preventing the development of a substrate for AF in response to increased atrial pressures.

In this issue of *Heart Rhythm*, Ramadeen and colleagues⁶ extend their group's work in the SAVP model.^{7,8} The authors now show that prophylactic ω 3-PUFA reduced the presence of inflammatory cells in the atria following 2 days of pacing. This result is consistent with a recent report from our laboratory documenting reduced atrial inflammation in dogs pretreated with ω 3-PUFA prior to cardiac surgery.⁹ Early atrial injury and inflammation may be a key step initiating the gene expression response to increased atrial pressure that promotes atrial structural remodeling, characterized by myocyte hypertrophy and the development of atrial fibrosis.

Concentrated ω 3-PUFA preparations are approved by the Food and Drug Administration for the treatment of hypertriglyceridemia, and the side-effect profile of these drugs is relatively benign. The efficacy of ω 3-PUFAs in modifying the substrate for AF when given *before* the development of experimental heart failure raises an obvious and important question. Would the administration of ω 3-PUFAs affect heart failure symptoms, atrial fibrosis, AF inducibility, or AF persistence when given *after* a sustained increase in atrial pressure?

Ramadeen et al⁶ also directly address this clinically important question. They report that when ω 3-PUFA treatment was initiated 7 days after the onset of tachypacing, treatment had no detectable impact on the extent of atrial fibrosis or atrial vulnerability to AF induced with burst pacing after 2 weeks of SAVP.

The authors previously reported that ω 3-PUFA pretreatment for 7 days prior to and 14 days following the onset of SAVP was associated with downregulation expression of hypertrophic and profibrotic genes (*Akt*, epidermal growth factor, *JAM3*, myosin heavy chain α -subunit, and *CD99*) in the treated relative to untreated control SAVP animals.¹⁰ In this study, they show that the first 7 days of SAVP were associated with increased atrial expression of *Akt*, SMAD7 (a profibrotic signaling molecule), and epidermal growth factor compared with unpaced animals. The early changes in gene expression may have been sufficient to initiate persistent changes in atrial gene expression. The initiation of ω 3-PUFA treatment after 7 days of pacing had no apparent impact on the expression of collagen isoforms I and III. Thus, to the extent that the beneficial effects of ω 3-PUFA treatment are dependent on a suppression of collagen expression, late initiation of treatment (for patients with significant atrial fibrosis) might be expected to have little benefit.

In addition to the lack of benefit with respect to atrial collagen expression profiles, the authors noted that ω 3-PUFA treatment was associated with a modestly increased risk of proarrhythmia in unpaced animals subjected to atrial burst pacing, with 21 days of treatment leading to an increase in episodes of tachyarrhythmia (>5-s duration) from ~1% to ~6% (Figure 5). In the absence of a hemodynamic load on the atria, this effect was unlikely to be due to a modification of atrial structure. While the significance of burst pacing as a trigger for AF might be questioned and no significant difference in AF incidence was detected, more serious ventricular proarrhythmic responses to ω 3-PUFA treatment have also recently been reported in dogs treated following myocardial infarction.¹¹

A large randomized clinical trial recently evaluated the impact of ω 3-PUFAs for the prevention of AF recurrence following cardioversion in groups of patients with either paroxysmal or persistent AF.¹² Somewhat surprisingly, this study reported no benefit of ω 3-PUFA treatment with respect to the recurrence of AF in patients with either paroxysmal or persistent AF. In view of the important results reported by Ramadeen et al, it seems likely that sufficient atrial structural remodeling had occurred prior to the onset of ω 3-PUFA treatment, limiting the potential for treatment benefit. In the presence of preexisting atrial

structural remodeling, accumulating clinical and preclinical evidence suggests that short-term dietary supplementation (weeks to months) with concentrated ω 3-PUFA preparations is unlikely to provide significant clinical benefit.¹³

Epidemiologic studies suggest that populations that consume more food-based ω 3-PUFAs (from plants or fish) and less ω 6-PUFAs have a lower incidence of AF and experience fewer cardiovascular deaths.¹⁴ Exercise has similar cardiovascular benefits.¹⁵ While dietary counseling and exercise programs are more difficult to implement and monitor, long-term programs that focus early and more holistically on modifying diet and lifestyle may have a greater impact on cardiovascular health than programs that narrowly focus on the acute pharmacologic modulation of ω 3-PUFA intake after the development of AF.

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