Polyunsaturated Fatty Acids in Heart Failure

To the Editor:
Coronary artery disease (CAD) and heart failure (HF) are low-grade systemic inflammatory conditions because the plasma levels of high sensitivity-C-reactive protein, interleukin-6 and tumor necrosis factor-α are elevated in these conditions.1 I showed that in CAD, hypertension, diabetes mellitus, hyperlipidemias, and obesity, diseases that predispose to the development of CAD and HF, the plasma phospholipid concentrations of arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are low.2 The study by Hara et al showed that low levels of serum polyunsaturated fatty acids (PUFAs), especially of n-3 EPA and DHA, are associated with worse HF-free survival in patients with acute myocardial infarction (AMI), and particularly with HF hospitalization and all-cause mortality.3 This finding suggests that the beneficial action of PUFAs in CAD and HF is related to their antiinflammatory properties, which also supports my proposal that PUFAs serve as predictors and prognostic markers of CAD.4 Hara et al5 did not supplement their study subjects with EPA/DHA and then examine whether such an intervention improved HF outcomes. Nor did they measure plasma and dietary AA levels and correlate them with HF-free survival in patients with AMI and with HF hospitalization and all-cause mortality. Such a study is necessary because a positive and negative feedback regulation exists between ω-3 (EPA and DHA) and ω-6 (AA) fatty acids.

AA and EPA form precursors to both pro- and antiinflammatory bioactive lipids. AA forms the precursor to pro-inflammatory 2-series prostaglandins (PGs) and thromboxanes (TXs) and 4-series leukotrienes (LTs) and antiinflammatory lipoxins (LXs). Similar products of the 3 series PGs and TXs and 5 series LTs are formed from EPA. PGs, TXs and LTs derived from EPA are less pro-inflammatory than those formed from AA, but are nevertheless pro-inflammatory in nature. Hence, the beneficial action of EPA and DHA observed in CHF and HF6 is unlikely to be related to the fatty acids themselves and/or formation of less pro-inflammatory PGs, TXs, and LTs, but could be related to the formation of antiinflammatory compounds, resolvins and protectins.5,6

Under normal physiological conditions, a balance is maintained between pro- and antiinflammatory substances. Thus, in CHF and HF a deficiency of antiinflammatory LXs, resolvins and protectins and an excess of pro-inflammatory PGs, TXs and LTs could exist. The low levels of serum EPA and DHA and their association with worse HF-free survival and all-cause mortality noted7 may be related to decreased formation of resolvins and protectins because of PUFA deficiency. In PUFA deficiency states, formation of pro-inflammatory PGs, TXs and LTs seems to be enhanced by the absence of the negative feed-back regulatory control exerted by LXs, resolvins and protectins. Such a proposal supports the suggestion that PUFAs and their antiinflammatory products reduce the burden of cardiovascular diseases in view of their HMG-CoA reductase and angiotensin-converting enzyme inhibitory, antiarrhythmic, antihypertensive, antiatherosclerotic, antiinflammatory, cytoprotective, and cardioprotective actions.7–9

Autonomic imbalance with increased adrenergic and reduced parasympathetic activity is involved in the development and progression of HF.10 Vagus stimulation reverses ventricular remodeling of the failing heart. Increasing parasympathetic activity stimulates endothelial nitric oxide generation. Right vagus stimulation in patients with advanced HF is feasible and safe and the consequent increased vagal tone improves the symptoms of HF and significantly increases the left ventricular ejection fraction. Acetylcholine, the principal vagal neurotransmitter, is a potent antiinflammatory molecule.11 These results suggest that activating antiinflammatory pathways in the form of vagal nerve stimulation is of benefit in CAD, HF and other inflammatory conditions.1,3,8,9 Secondary hypertension induces downregulation of the α7 nicotinic acetylcholine receptor (α7nAChR) and decreased expression of α7nAChR contributed to inflammation in the 2-kidney 1-clip hypertensive rat model, suggesting that hypertension is also a low-grade systemic inflammatory condition12 in which vagal tone is reduced.13

Because acetylcholine and LXs, resolvins and protectins have antiinflammatory actions, it is likely that acetylcholine and vagal nerve stimulation augment the production of LXs, resolvins and protectins and thus bring about their antiinflammatory actions. This is supported by the observation that a linoleic acid derivative, DCP-LA, ameliorated the learning and memory impairment by targeting the α7nAChR14 and that PUFAs enhance acetylcholine levels in the brain and other tissues.15,16

Hence, studying the roles of LXs, resolvins, protectins and acetylcholine and vagal tone in the pathobiology of CAD and HF may prove to be interesting.

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