Editorial

Metabolic therapies for heart disease: Fish for prevention and treatment of cardiac failure?

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See article by Takahashi et al. [2] (pages 213–223) in this issue.

There are a myriad of structural and biochemical abnormalities associated with the failing heart, yet the hallmark of this syndrome is the inability to effectively transfer the chemical energy from foodstuffs to the mechanical energy of left ventricular ejection against aortic pressure. The causes and consequences of dysfunctional energy metabolism in heart failure are poorly understood; nevertheless, there is growing evidence to suggest that alterations in energy substrate metabolism contribute to cardiac hypertrophy, left ventricular remodeling, and systolic dysfunction. Present medical therapies for heart failure act via suppression of neurohormonal activation (e.g. β-adrenergic receptor antagonists, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and aldosterone receptor antagonists), reducing volume overload (diuretics), or hemodynamic symptoms (inotropic agents). Despite optimal treatment with current drugs, most patients continue to deteriorate, and the prognosis remains poor; thus, additional effective therapies are needed that act independent of the neurohormonal/hemodynamic axis [1]. Nutritional therapies and pharmacological modulation of energy metabolism are particularly attractive because they could work additively with current therapies while not exerting negative hemodynamic effects [1].

In this issue of Cardiovascular Research, Takahashi et al. present the interesting finding that dietary supplementation with fish oil attenuates the development of hypertrophic cardiomyopathy and prolongs life in mice with carnitine deficiency [2]. Moreover, they found that ingestion of fish oil differentially altered the myocardial concentrations of various diacylglycerols and prevented diacylglycerol-induced activation of protein kinase C (PKC) isoforms α, β2, and ε by reducing their translocation from the cytosol to the plasma membrane. Chronic PKC activation has been linked to cardiac hypertrophy and development of heart failure [3]; thus, these findings suggest the possibility that consumption of fish oil could reduce the risk for development of hypertrophic cardiomyopathy and/or heart failure.

Further support for this concept comes from a recent, large epidemiological study that assessed people over a 12-year period, demonstrating a 31% reduction in the risk for developing heart failure in individuals consuming fish three to four times per week compared to those eating fish only once a month or less [4]. In addition, consumption of fried fish was positively associated with incident heart failure, while intake of long-chain n-3 fatty acids was inversely associated with heart failure. Heart failure is not a simple disease, but rather a complex clinical syndrome with multiple etiologies and symptoms, many of which can be affected by fish oil consumption. Clinical studies have shown that consumption of fish oils and polyunsaturated fatty acids can reduce the occurrence of ischemic heart disease and sudden cardiac death [5,6]. Consump-
Fish oils reduce the frequency of atrial fibrillation and ventricular arrhythmias [6,7], arterial wall stiffness and blood pressure [8,9], plasma triglyceride concentration [5], and can increase the ratio of external cardiac power at a given myocardial oxygen consumption [10] (Fig. 1). All of these effects should decrease the risk for cardiac hypertrophy and/or the development of heart failure. In addition, fish oils can activate peroxisome proliferator activated receptors [11], which could induce anti-inflammatory actions and improve myocardial metabolic function. While a prospective clinical trial has not been performed to assess the effects of fish oil in prevention and treatment of heart failure or hypertrophic cardiomyopathy, current data suggest that consumption of fish oils could be an effective therapy.

Recent studies suggest that other metabolic therapies are promising for the treatment of heart failure. Clinical studies in heart failure patients with a history of myocardial ischemia show that long-term treatment with the fatty acid beta-oxidation inhibitor trimetazidine improves ventricular function and exercise tolerance [12,13]. Similar effects were observed with the partial fatty acid oxidation inhibitor ranolazine in dogs with heart failure [14]. In addition, we recently reported in this journal that pharmacological inhibition of mitochondrial fatty acid uptake early in the development of canine heart failure prevents left ventricular wall thinning and delays the rate of progression to end-stage heart failure [15].

At present, definitive clinical trials have yet to be performed with metabolic drugs or nutritional therapies in heart failure patients. Nevertheless, these approaches have great potential for the prevention and treatment of heart failure. In the face of recent evidence on the effectiveness of dietary fish oils and polyunsaturated fatty acids in the prevention of cardiac death [5,6], prospective evaluation of this approach is warranted as adjunctive therapy in treatment of heart failure.

References


