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Review article

ω3-Polyunsaturated fatty acids for heart failure: Effects of dose on efficacy and novel signaling through free fatty acid receptor 4

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ABSTRACT

Heart failure (HF) affects 5.7 million in the U.S., and despite well-established pharmacologic therapy, the 5-year mortality rate remains near 50%. Furthermore, the mortality rate for HF has not declined in years, highlighting the need for new therapeutic options. Omega-3 polyunsaturated fatty acids (ω3-PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are important regulators of cardiovascular health. However, questions of efficacy and mechanism of action have made the use of ω3-PUFAs in all cardiovascular disease (CVD) controversial. Here, we review recent studies in animal models of HF indicating that ω3-PUFAs, particularly EPA, are cardioprotective, with the results indicating a threshold for efficacy. We also examine clinical studies suggesting that ω3-PUFAs improve outcomes in patients with HF. Due to the relatively small number of clinical studies of ω3-PUFAs in HF, we discuss EPA concentration-dependency on outcomes in clinical trials of CVD to gain insight into the perceived questionable efficacy of ω3-PUFAs clinically, with the results again indicating a threshold for efficacy. Ultimately, we suggest that the main failing of ω3-PUFAs in clinical trials might be a failure to reach a therapeutically effective concentration. We also examine mechanistic studies suggesting that ω3-PUFAs signal through free fatty acid receptor 4 (Ffar4), a G-protein coupled receptor (GPR) for long-chain fatty acids (FA), thereby identifying an entirely novel mechanism of action for ω3-PUFA mediated cardioprotection. Finally, based on mechanistic animal studies suggesting that EPA prevents interstitial fibrosis and diastolic dysfunction, we speculate about a potential benefit for EPA-Ffar4 signaling in heart failure preserved with ejection fraction.

Contents

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; HHD, hypertensive heart disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; EF, ejection fraction; ω3-PUFA, omega 3 polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid; FA, fatty acid; GPR, g-protein coupled receptor; Ffar, free fatty acid receptor; ECM, extracellular matrix; MMP, matrix metalloproteinase; TIMP, tissue inhibitors of metalloproteinases; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; cGMP, cyclic guanosine monophosphate; Smad, mothers against decapentaplegic, drosophila, homolog of; PKG, protein kinase G; MCP-1, monocyte chemoattractant protein-1; ADMA, asymmetric dimethylarginine; TAC, transverse aortic constriction; αSMA, α-smooth muscle actin; TGFβ1, transforming growth factor β1.

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1. Introduction

Heart failure (HF) affects approximately 5.7 million people in the U.S. at an annual cost of nearly 30 billion dollars, and this is estimated to increase to nearly 9 million people at a cost of nearly 80 billion dollars by 2030 [1]. Despite a well-defined pharmacological therapeutic regimen that includes β-adrenergic receptor blockers, angiotensin converting enzyme inhibitor/angiotensin receptor blockers, diuretics, and aldosterone antagonists, the five-year mortality rate is still greater than 50% [1]. Furthermore, the mortality rate for HF has not declined in years, highlighting the unmet need for new therapeutic options.

Omega-3 polyunsaturated fatty acids (ω3-PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are important regulators of cardiovascular health [2,3]. Several clinical trials have demonstrated that ω3-PUFAs confer a survival benefit in coronary heart disease (CHD) by preventing sudden death [4–8], and more recently clinical trials have indicated that ω3-PUFAs might improve outcomes in HF [9–13]. Despite these potential benefits, the use of ω3-PUFAs in CHD and HF remains controversial.

Here, we review evidence from basic studies in animal models of HF and clinical trials with ω3-PUFAs in HF that suggest that ω3-PUFAs, particularly EPA, improve HF outcomes. Further, we examine data from animal models of HF suggesting a relationship between EPA concentration and cardioprotection, observed as prevention of interstitial fibrosis and diastolic dysfunction. Due to the relatively small number of clinical studies of ω3-PUFAs in HF, we review the relationship between EPA concentration and cardiovascular disease (CVD) outcomes to gain insight into the perceived questionable efficacy of ω3-PUFAs clinically. Ultimately, we suggest that the main failing of ω3-PUFAs in clinical trials might be a failure to reach a therapeutically effective concentration. Additionally, we review data suggesting that ω3-PUFAs signal through free fatty acid receptor 4 (Ffar4), a G-protein coupled receptor (GPR) for long-chain fatty acids (FA). We suggest that Ffar4 might mediate the cardioprotective benefits of EPA in the heart, proposing an entirely novel mechanism of action for ω3-PUFA mediated cardioprotection. Finally, based on data indicating that EPA prevents interstitial fibrosis and diastolic dysfunction in an animal model of HF, we speculate about a potential benefit for EPA-Ffar4 signaling in heart failure preserved with ejection fraction (HFpEF).

2. ω3-PUFAs in HF, a potential new therapeutic target

2.1. ω3-PUFAs in dietary advice, dietary supplementation, and pharmacotherapy

ω3-PUFAs, EPA and DHA, in health and disease are addressed via dietary advice, dietary supplementation, and pharmaceutical applications. They are prolifically studied in all three settings and guidelines exist for each in many nations. Most generally, dietary advice is aimed at good overall health, dietary supplementation is meant to manage present or latent risk, and pharmaceutical application is directed toward clinically indicated risk markers. Global recommendations are cataloged by the International Society for the Study of Fatty Acids and Lipids (ISSFAL) on behalf of the Global Organization for EPA and DHA (GOED), and include general health recommendations by national authoritative bodies as well as recommendations for supplementation by expert societies; Brownawell et al. provide a detailed assessment of advice and the regulatory environment [14]. For prevention of cardiovascular disease, the National Heart Lung and Blood Institute (NHLBI) recommends increasing ω3-PUFAs through a general increase of seafood intake.[2] Currently, both ISSFAL[3] and the American Heart Association (AHA) recommend ω3-supplementation (0.5 g/d and 1 g/d respectively) for patients with CHD, citing benefits including lowering of triglycerides, prevention of arrhythmias, and prevention of atherosclerosis. Here, we will review current basic and clinical research suggesting the potential for ω3-PUFAs in HF.

2.2. ω3-PUFAs in animal models of HF

Few studies have examined ω3-PUFAs in HF, particularly from a mechanistic standpoint in cultured cells or animal models of HF, although a handful of studies have demonstrated various positive effects of ω3-PUFA-supplementation [15–19]. Yet, very few studies have examined the cellular and molecular mechanisms whereby ω3-PUFAs are cardioprotective.

Recently, we reported that dietary supplementation with an ω3-PUFA-rich diet prevented cardiac dysfunction and interstitial fibrosis induced by surgical constriction of the transverse aorta (TAC) in mice [20]. TAC is a common HF model in which ventricular remodeling is characterized by hypertrophy, systolic and diastolic dysfunction, and interstitial cardiac fibrosis. We found that 12 weeks of dietary supplementation with an ω3-rich diet significantly increased ω3-levels in blood and heart tissue to levels slightly higher than normally achieved in treated patients in the US (ω3-index = 15.2%, defined as ([%DHA + %EPA] / total FA) in erythrocytes) [20]. Functionally, ω3-PUFA supplementation prevented TAC-induced systolic and diastolic dysfunction. At the tissue level, ω3-PUFAs prevented TAC-induced

[2] http://www.nhlbi.nih.gov/health-pro/guidelines/current/cardiovascular-health-pediatric-guidelines/full-report-chapter-5.

[3] International Society for the Study of Fatty Acids and Lipids (June 2004). Report of the Sub-Committee on Recommendations for Intake of Polyunsaturated Fatty Acids in Healthy Adults. [online] Available at: http://www.issfal.org/news- links/resources/publications/PUFAIntakeReccomdFinalReport.pdf.