fibrosis and, consequently, ventricular dysfunction. Inhibition of collagen remodeling can lead to improved cardiac function, demonstrating the relevance of new insights into the compensatory remodeling mechanism. Thus, our findings give new theoretical support for the treatment of patients with ischemic cardiomyopathy.

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Omega-3 Highly Unsaturated Fatty Acids and Arrhythmia Risk
Influences of Load Conditions and a Differential Endogenous Metabolism

We read with great interest the recent report by Nigam et al. (1) about the AFFORD (Multi-Center Study to Evaluate the Effect of n-3 Fatty Acids [Omega-3] on Arrhythmia Recurrence in Atrial Fibrillation) trial. Supplementation of 4 capsules fish oil per day (containing a total of 1,600 mg eicosapentaenoic acid, 20:5n-3, and 800 mg docosahexaenoic acid [DHA], 22:6n-3) was shown not to reduce recurrence of atrial fibrillation. In parallel, markers of inflammation or oxidative stress were not affected. Up to now, numerous studies have provided a large variety of potential effects attributed to highly unsaturated fatty acid (HUFA) treatment ranging from marked prognostic improvements in heart failure and antiarrhythmogenic actions to no incremental effects. Due to the divergent results, the question arises whether mechanisms exist beyond an external HUFA intake.

In heart failure, an inverse shift of serum fatty acids occurs; particularly saturated and mono-unsaturated fatty acids were increased, whereas poly- and highly unsaturated omega-6 and omega-3 fatty acids were decreased (2,3). We have recently shown that increased ventricular wall stress is associated with reduced DHA levels (unpublished data, P. Alter, January, 2015). Similar, but less pronounced effects were found for eicosapentaenoic acid and arachidonic acid (20:4n-6). Because the liver is the major source of endogenous HUFA, pseudocholinesterase activity, a marker of hepatic metabolizing capacity, was examined and shown to be inversely correlated with increased end-diastolic and end-systolic ventricular wall stress, which emphasizes the hypothesis of a cardio-hepatic syndrome (e.g., influenced by congestion). In addition, local variances of the endogenous HUFA metabolism leading to inhomogeneities of HUFA concentrations and effects should be considered.

It was previously shown that systemic HUFA levels in red blood cells and plasma correlate with right atrial concentrations. Oral HUFA supplementation was incorporated into the atrial myocardium (4). However, little is known about cardiac influences on myocardial HUFA levels (5). We recently found significant differences of DHA concentrations among atrial and ventricular myocardium in experimental animals by using gas chromatography/mass spectrometry (atrium 4.69 ± 1.02% vs. ventricle 8.99 ± 2.05%; p < 0.001) (unpublished, P. Alter, January, 2015). It is suggested that different load conditions, in particular increased wall stress, are involved. Because DHA exhibits antiarrhythmogenic actions, the question arises whether reduced atrial DHA levels account for an increased risk of atrial fibrillation. Of note, intermediate DHA
metabolism products, particularly tetracosapentaenoic acid (24:5n-3) and tetracosahexaenoic acid (24:6n-3), were increased in atrial, but not in ventricular myocardium after intrapericardial HUFA administration, which was associated with a higher ventricular potential to finalize DHA synthesis. Tetracosahexaenoic acid requires carnitine octanoyltransferase, a family member of carnitine acyltransferases, for transportation into the endoplasmic reticulum to undergo final beta-oxidation. It was previously shown that carnitine palmitoyltransferase (1b and 2) is reduced in atrial compared with ventricular myocardium. It is proposed to evaluate beta-oxidation as a novel target for endogenous HUFA concentrations. In accordance with the report by Nigam et al. (1), no changes of HUFA levels were found after a challenge with the proinflammatory peroxisome proliferator-activated receptor-alpha agonist fenofibrate or in a talcum-induced pericarditis model.

Up to now, involvement of cardiac load conditions and the differential endogenous HUFA metabolism were not sufficiently taken into account, which may provide a rationale for divergent findings of HUFA treatment in previous trials.

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REFERENCES

Applying Cluster Analysis to Data of Previously Published Chronic Heart Failure Trials

I enjoyed studying the contribution by Ahmad et al. (1), and the accompanying editorial by Francis et al. (2), published in the October 28, 2014 issue of the Journal, about the application of cluster analysis to the data from 1,619 participants of HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study. The investigators reported that cluster analysis provided an advantage over traditional phenotyping, based on the subjective symptomatic assessment of the patients via the New York Heart Association functional classification I to IV, and A to D stages, and imaging-based left ventricular ejection fraction (LVEF) in predicting outcomes (all-cause and cardiovascular, mortality, and hospitalization risks) and response to surrogate parameters (change in peak oxygen consumption and in standard 6-min walk test). Clinicians following longitudinally large numbers of heart failure (HF) patients with a reduced LVEF in cardiology clinics have long been accustomed to the incongruity between the functional classification/staging (New York Heart Association class II to IV) and LVEF (≤35%) and outcomes of their patients, stemming from our current coarse phenotyping of a highly heterogeneous disease as HF and the impact of comorbidities.

Ahmad et al. (1) arbitrarily employed 45 pre-specified clinical variables and identified 4 phenotypic clusters, with intracluster similarities and intercluster differences, in which they showed diverse mortality and hospitalization rates. It is of interest that in the exhaustive list of variables used (1), a measure of the patients’ overall compliance with their management in general, and with drug taking in particular, is missing (issues of frequent concern in cardiology clinics), for which the investigators are not responsible. Ahmed et al. (1) and Francis et al. (2) cited the reasons why a number of trials (refs. 7, 8, and 35 in Ahmed et al.[1]) and patients with HF with a reduced LVEF (refs. 5 to 8 in Francis et al.[2]) “have failed to meet their endpoints” (2), and Ahmed et al. (1) stated that “we have seen such little progress in developing new treatments for this disorder.”

Although we need to adopt the philosophy of enhanced and refined phenotyping in designing future HF clinical trials (2), what should have