Failure of omega-3 fatty acids in atrial fibrillation? No deficiency of highly unsaturated fatty acids in the absence of heart failure

The trial of Bianconi et al. using high-dose treatment with n-3 highly unsaturated fatty acids (HUFAs) ethyl esters failed to demonstrate a difference from placebo in recurrence of atrial fibrillation (AF). Since AF remains a prevalent disease and drug or ablation therapies are not uniformly effective, the identification of causes for the mixed outcome of this and previous trials remains an urgent need. A most likely cause relates to the presence and severity of structural heart disease. Cardiac dilatation and dysfunction remain underrated influences on HUFA metabolism. In the trial, marked structural heart disease was not present as deduced from the LV end-diastolic diameter (LVEDD) 51.4 ± 6.2 mm, left ventricular ejection fraction (LVEF) 57.7 ± 11.3% and 25.7% of patients being in New York Heart Association (NYHA) class II–III. Thus, overall, patients were not expected to exhibit HUFA deficiency that would require substitution. We have shown in 308 patients (NYHA class 2.2 ± 0.6, LVEF 31 ± 10%) that an increase in LVEDD (68–90 vs. 48–61 mm) was associated with reduced serum docosahexaenoic acid (DHA) (1.0 ± 0.5 vs. 1.3 ± 0.6%) and arachidonic acid (4.6 ± 1.8 vs. 5.2 ± 1.9%). A low DHA (0.01–0.9%, lower tertile vs. 1.4–3.1%, upper tertile) was associated with greater (left ventricular dilatation (LVEDD 67.4 ± 7.5 vs. 63.2 ± 6.8 mm). The negative predictive value for severe dilatation was 91% and sensitivity was 84%. Only few patients with DHA > 1.24% exhibited severe LV dilatation. Paradoxically, factors that promote risk of dilatation reduce HUFA. A low n-3 HUFA is expected to be also associated with a reduced occupancy of the n-3 fatty acid receptor GPR120 with anti-inflammatory and insulin-sensitizing action.

Furthermore, treatment with n-3 HUFA ethyl esters improved heart function and reduced dilatation in patients (LVEDD 67.4 ± 6.9 mm, LVEF 36 ± 7%) with non-ischemic dilative cardiomyopathy. The patients in the present trial were, however, not stratified according to LVEDD or LVEF. Some of the patients did most probably also not have an arrhythmic stratum that is a target for n-3 HUFA, e.g. stretch-induced AF or heart failure-induced atrial structural remodelling and AF promotion. In this context, also the duration of AF prior to cardioversion is crucial, since long-term atrial fibrillation leads to adverse atrial remodelling which ‘begets’ chronic fibrillation. We conclude that the divergent findings of AF trials can at least in part be attributed to the presence of HUFA deficiency of variable severity. A meta-analysis taking into account influences of heart dysfunction on the efficacy of n-3 HUFA would greatly advance our knowledge.

For the present trial, we suggest to assess whether links exist between the efficacy of administered n-3 HUFA and heart dysfunction and increased wall stress associated with chamber dilatation and arrhythmias. In view of the finding that patients awaiting coronary artery bypass surgery had previously benefited from n-3 HUFA, the question should also be addressed whether links with ischaemic heart disease exist. Since ischaemia is expected to release HUFA from membrane phospholipids via sympathetic activation, it could amplify the level of free n-3 HUFA that arises from the sustained intestinal absorption of n-3 HUFA ethyl esters.

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References

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Response to letter: ‘Failure of omega-3 fatty acids in atrial fibrillation? No deficiency of highly unsaturated fatty acids in the absence of heart failure’

We thank Drs Heinz Rupp and colleagues for their interest in our paper. The authors refer to their study in which left ventricular (LV) dilatation was found to be associated with vulnerability to atrial fibrillation in a rabbit model. J Cardiovas Electrophysiol 2005;16:1189–94.

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