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Clinical Research

From Heart Failure to Highly Unsaturated Fatty Acid Deficiency and Vice Versa: Bidirectional Heart and Liver Interactions

Peter Alter, MD,[a] Tobias Glück, MD,[a] Jens H. Figiel, MD,[b] A. Rembert Koczulla, MD,[a] Claus F. Vogelmeier, MD,[a] and Heinz Rupp, PhD[a,†]

[a] *Department of Medicine, Pulmonary and Critical Care Medicine, University of Marburg, Marburg, Germany*

[b] *Department of Radiology, University of Marburg, Marburg, Germany*

ABSTRACT

Background: In several trials, beneficial prognostic effects of highly unsaturated fatty acids (HUFAs) in heart failure were shown. Because other studies showed no incremental benefit in nearly preserved cardiac function, the question arises, whether the degree of cardiac dysfunction is involved. It is hypothesized that increased left ventricular (LV) wall stress affects the endogenous hepatic HUFA metabolism, which in turn exhibits adverse cardiac consequences.

Methods: Cardiac magnetic resonance imaging was performed in 30 patients with suspected cardiomyopathy. The serum fatty acid profile was assessed using gas chromatography/mass spectrometry.

Results: Docosahexaenoic acid (DHA; $P = 0.002$) and eicosapentaenoic acid (EPA; by trend) levels were decreased in patients with reduced LV ejection fraction ($\leq$ 50%) or LV dilatation ($\geq$ 90 mL/m^2). Decreased DHA ($P = 0.003$) and EPA ($P = 0.022$) levels were associated with a reduced LV ejection fraction. Decreased DHA level was

RÉSUMÉ

Introduction : Plusieurs essais, thérapeutiques ont montré des effets pronostiques bénéfiques des acides gras hautement insaturés (AGHI) dans l'insuffisance cardiaque. En raison d'autres études qui n'ont montré aucun bénéfice supplémentaire sur la fonction cardiaque préservée, la question se pose de savoir si le niveau de dysfonction cardiaque est en cause. L'hypothèse d'une augmentation du stress du mur ventriculaire gauche (VG) affecte le métabolisme hépatique endogène des AGHI, qui aura à son tour des répercussions cardiaques indésirables.

Méthodes : L'imagerie cardiaque par résonance magnétique a été réalisée chez 30 patients avec suspicion de cardiomyopathie. Le profil des acides gras sériques était évalué par chromatographie en phase gazeuse/spectrométrie de masse.

Résultats : Les niveaux d'acide docosahexaénoïque (ADH; $P = 0{,}002$) et d'acide eicosapentaénoïque (AEP; avec une tendance) ont diminué

Even with application of current guideline-adjusted therapy, progression of heart failure, when it exists beyond a certain degree, often cannot be prevented. Worsening of heart failure is characterized by cardiac dilatation and reduced ventricular pump function. Increased left ventricular (LV) wall stress is a crucial prognostic determinant that leads to progression of dilatation and increased risk of sudden cardiac death. Increased omega-3 fatty acid concentrations were associated with a decreased incidence of congestive heart failure.[1] In several trials, beneficial prognostic effects have been attributed to the treatment with highly unsaturated fatty acids (HUFAs).[2,3] Concerns arose when studies on patients with nearly preserved cardiac function showed no incremental benefit.[4-7] A meta-analysis of 14 randomized, double-blind, placebo-controlled trials involving 20,485 patients showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.[8] Because of these inconclusive findings, it was suggested that patient-specific factors are crucially involved. It was hypothesized that the efficacy of HUFA therapy depends on the degree of cardiac dysfunction.[9]

An inverse shift in the serum fatty acid profile was recently shown in heart failure.[10] Particularly, the omega-3 docosahexaenoic acid (DHA; 22:6n-3, $C_{21}H_{31}COOH$) and the omega-6 arachidonic acid (20:4n-6, $C_{19}H_{31}COOH$) levels were reduced in patients with LV dilatation[10]; in contrast, monounsaturated and saturated fatty acid levels were increased.[11] A similar but less pronounced fatty acid shift was

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†Deceased.

Corresponding author: Dr Peter Alter, Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-University Marburg, Germany, Member of the German Center for Lung Research (DZL), Baldingerstrasse, 35033 Marburg, Germany. Tel.: +49-6421-5866140; fax: + 49-6421-5866149.

E-mail: alter@uni-marburg.de

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correlated with increased end-diastolic ($P = 0.047$) and end-systolic LV wall stress ($P = 0.001$). Pseudocholinesterase activity was inversely correlated with end-diastolic ($P = 0.020$) and end-systolic LV wall stress ($P = 0.025$).

Conclusions: DHA level was significantly reduced in heart failure. Similar, but less pronounced effects were found for EPA and arachidonic acid by trend. Increased LV wall stress was correlated with a reduced DHA level. Increased LV wall stress exhibits various adverse consequences (eg, increased oxygen consumption, favouring of arrhythmias, and an unfavourable remodelling). The increase of wall stress was paralleled by reduced HUFA level. Increased LV wall stress was correlated with reduced pseudocholinesterase, which is suggestive of hepatic congestion (ie, a cardiohepatic syndrome, involved in the altered fatty acid profile in heart failure) and has major consequences regarding the dose-efficacy of HUFA treatment.

chez les patients avec réduction de la fraction d'éjection du VG ($\leq$ 50 %) ou dilatation du VG ($\geq$ 90 ml/m^2). Une diminution des niveaux de ADH ($P = 0{,}003$) et d'AEP ($P = 0{,}022$) a été associée à une fraction d'éjection du VG réduite. Une diminution de taux de ADH était corrélée à une augmentation du stress du VG en fin de diastole ($P = 0{,}047$) et en fin de systole ($P = 0{,}001$). L'activité pseudocholinestérase était inversement corrélée avec un stress du VG en fin de diastole ($P = 0{,}020$) et en fin de systole ($P = 0{,}025$).

Conclusions : Le taux de ADH était significativement réduit en insuffisance cardiaque. Des effets similaires, suivant la même tendance, mais moins prononcés, ont été trouvés pour l'AEP et l'acide arachidonique. Une augmentation du stress du VG a été corrélée avec un taux réduit de ADH. Une augmentation du stress du VG présente diverses répercussions indésirables (par exemple, une augmentation de la consommation d'oxygène, favorisant les arythmies, et un remodelage nocif). L'augmentation du stress de la paroi était accompagnée d'un niveau réduit des AGHI. Une augmentation du stress du VG a été corrélée avec une pseudocholinestérase réduite, ce qui évoque une congestion hépatique (c.-à-d., un syndrome cardiohépatique impliqué dans un profil d'acides gras modifié en cas d'insuffisance cardiaque) et a des conséquences majeures concernant la relation dose-efficacité du traitement par AGHI.

induced by sympathetic activation in experimental animals. Thus, it was assumed that mechanisms associated with a depressed cardiac function and chamber dilatation are involved.

Besides a food-derived external intake, the endogenous fatty acid metabolism involves steps of chain elongation and desaturation became of major interest. It was shown that the delta5-desaturase activity, which is crucially involved in the HUFA synthesis, was reduced in severely impaired LV function.[11] Peroxisomal β-oxidation was recently identified to account for myocardial HUFA concentration. Because the liver is the major source of endogenous HUFA, potential determinants linking heart failure to liver metabolism were examined in the present study.

It was hypothesized that increased LV wall stress affects the endogenous hepatic HUFA metabolism, which in turn exhibits adverse cardiac consequences. Therefore, the fatty acid profile including saturated fatty acids, mono- and polyunsaturated fatty acids, and highly unsaturated long-chain DHA, eicosapentaenoic acid (EPA; 20:5n-3, $C_{19}H_{29}COOH$), and arachidonic acid were examined. As a surrogate marker of hepatic metabolizing capacity, pseudocholinesterase (PCHE) activity was measured. For analysis of LV wall stress, cardiac magnetic resonance (CMR) imaging was performed to accurately measure cardiac volumes, and myocardial mass and function.[12]

Methods

A total of 30 Caucasian patients with suspected idiopathic cardiomyopathy were enrolled in the study. Patients had been admitted because of chronic left heart failure, chest pain, or exertional dyspnea. Severe coronary artery and valvular heart disease had been excluded. Details are summarized in Supplemental Table S1. All patients underwent CMR imaging for further evaluation. Thereby, ventricular volumes, mass, function, and myocardial morphology were assessed. Patients with active myocarditis, other inflammatory or autoimmune diseases (eg, sarcoidosis or Churg-Strauss syndrome), and patients with storage diseases (eg, amyloidosis), patients with primary right heart failure, malignancies, severe kidney and apparent liver disease were not included. Patients received guideline-adjusted heart failure therapy as appropriate, exclusive of HUFA supplementation. As part of the standard routine blood profile captured in the supine position under resting and fasting conditions, creatinine, blood urea nitrogen, serum albumin, aspartate and alanine amino transferase levels were assessed. PCHE activity, a serum marker of hepatic metabolizing capacity,[13,14] was obtained in a subgroup of 21 patients using photometry (normal range for patients of at least 16 years of age: 5860-13,000 U/L). The study was in accordance with the institutional guidelines.

CMR-based measurement of LV volume, myocardial mass, and wall stress

CMR imaging (1.5 T; Siemens, Erlangen, Germany) was performed in all patients. To obtain LV volumes (end-diastolic volume [LVEDV], and end-systolic volume [LVESV]), function (ejection fraction [LVEF]) and myocardial mass, a stack of short-axis views of the left ventricle from base to apex was acquired using electrocardiogram-gated steady-state free precession sequences (TrueFISP).[15,16] Wall stress was calculated using a thick-walled sphere model of the left ventricle.[12,17] The method was primarily derived from the law of LaPlace, but allows wall stress calculation for arbitrary wall diameters. For calculation of the wall stress index at end-diastole and end-systole, LV cavity and myocardial volumes were inserted as measured using CMR imaging.[18] Wall stress was obtained by multiplication of the wall stress index with pressure. Therefore, an intraventricular pressure of 16 mm Hg at end-diastole and 130 mm Hg at end-systole was assumed for approximation as previously described in detail.[18]