Immune-metabolome response to an acute exercise exertion reveals dysfunctional metabolic recovery in heart failure

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Background: Patients with heart failure with reduced ejection fraction (HFrEF) have an increased inflammatory load and impaired cardiac oxidative lipid phosphorylation. Early dysregulations of pathophysiological alterations may not be detectable if patients are assessed under resting conditions.

Purpose: We exposed HFrEF patients to a physical exertion challenge by cardiopulmonary exercise testing (CPET) and determined inflammatory and metabolic parameters before, during and 2 hours after the test.

Methods: A symptom-limited CPET was performed in participants with HFrEF (n = 16) and age and sex matched controls (CON, n = 13). In addition to clinical and physiological parameters, we assessed blood counts of leukocyte subtypes, their morphology, aggregation with platelets and microvesicle release, as well as plasma cytokines and metabolites at baseline (T1), immediately after CPET (T2), and after 2 hours of rest (T3). Inflammatory and metabolic parameters were measured using the ThermoFischer ProcartaPlex Human Inflammation-Panel and Biocrates MxP® Quant 500 kit, respectively. Non-parametric tests were chosen and all multiple tests were adjusted by the Benjamini-Hochberg method.

Results: Cardiovascular risk profile of HFrEF and CON was similar. In agreement with the definition for HFrEF, these patients had a lower EF and a greater left ventricular enddiastolic diameter compared to CON. There were no differences between groups for leukocyte, cytokine or metabolic parameters at T1. Immediately after CPET, 20 parameters were significantly increased in both groups, including an increase of lactate, natural killer (NK) and NK T cell blood counts. In addition, 131 inflammatory and metabolic parameters were upregulated only in HFrEF, as compared to only 17 in CON. In HFrEF-platelet aggregates with NK cells, CD8+ cytotoxic T cells and "classical" CD14++CD16- monocytes, 58 different phosphatidylcholines and 21 triglycerides were upregulated immediately after exercise. At T3 almost all altered parameters returned to baseline in CON while in HFrEF blood counts and morphological markers of inflammatory effector cell types, including NK cells, CD8+ T cells and neutrophils, as well as genomic nuclear DNA, an indicator of cell death, remained elevated. Moreover, several triglycerides did not return to baseline in HFrEF after a 2-hour resting period. In these patients, but not in CON, the different lipids (i.e. phosphatidylcholine, triglycerides) strongly correlated with pro-inflammatory cytokines and NK cells.

Conclusion: Our data support the concept of impaired fatty acid utilization and inflammation-mediated metabolic dysregulation in HFrEF. However, the correlations between metabolic and inflammatory parameters were not detected at baseline in comparison to a control group with similar cardiovascular risk profile. Therefore, investigating patients in response to a physical or metabolic challenge might reveal early pathological changes.