Rozdział 7. Summary

Heart failure (HF) is a common clinical syndrome which constitutes the final stage of a variety of cardiovascular diseases. Despite significant improvement in the HF treatment (e.g. beta blockers, ACE-inhibitors, aldosterone antagonists – MRA, ivabradine, cardiac resynchronization therapy), prognosis of those patients remains poor. To improve our understanding of the molecular mechanisms underlying the heart failure – a multisystemic disease – not only cardiac metabolism perturbations but also metabolic derangements of other organs should be taken into consideration. Metabolomics enables simultaneous qualitative and quantitative identification of a maximum number of metabolites present at a particular time point. Therefore metabolomics gives a possibility to identify blood metabolites profile characteristic to the particular disease that may potentially have a predictive value and could be in the future a reference point in assessing the effectiveness of the therapy that had been implemented. The possibility of obtaining material for testing by using peripheral blood is an additional advantage of metabolomics.

The aim of the study was to identify changes in the blood metabolites profile, occurring as a result of HF with the use of untargeted metabolomics.

The study included 67 ambulatory optimally treated patients with a minimum of six-month history of chronic heart failure with typical clinical symptoms (hemodynamic class NYHA II-III), echocardiographically confirmed impaired LV systolic function (left ventricular ejection fraction - LVEF $\leq$35%), irrespectively of the HF etiology. The control group consisted of 39 volunteers with clinically, biochemically and echocardiographically excluded heart failure who were treated as outpatients for hypertension, atrial fibrillation, ischemic heart disease, hypercholesterolemia. The following exclusion criteria were applied: lack of consent, a history of implantation of the cardiac resynchronization therapy device (CRT), diagnosis of cancer in the past five years, acute and chronic inflammatory diseases (rheumatoid arthritis and asthma), severe renal dysfunction (estimated glomerular filtration rate – eGFR <30ml/min/1.73m2), diabetes mellitus, thyroid dysfunction requiring pharmacotherapy, HF exacerbation in the last month, severe COPD (chronic obstructive pulmonary disease; forced expiratory volume in one second - FEV1 less than 50% of a predicted value). The analyses were performed first in the derivation set (36 chronic HF patients and 19 age-matched controls without the disease) and repeated in validation cohort (31 chronic HF patients and 20 age-, gender-, BMI-, IHD occurance- and statin use-matched controls). Metabolomic analysis

was performed on serum samples collected in the morning after compulsory fasting at the time of enrollment to the study.

Independent analyses of both sets revealed statistically significant decline in intensities of phosphatidylcholine (PC): 34:4 and 36:5, lysophosphatidylcholine (lyso-PC): 14:0, 15:0, 18:0, 18:2, 20:3, lysophosphatidylethanolamine (lyso-PE): 18:1 and 18:2 in chronic HF patients. More symptomatic patients and those with ischaemic etiology of HF presented greater deficit in phospholipids (PLs) intensities. In addition, the percentage of deficiency in most of the statistically significant PLs (calculated in relation to the mean/median intensity of a particular metabolite in the control group) was associated with lower total cholesterol level, impaired renal function, reduced exercise tolerance, increased exercise respiratory response and parameters associated with impaired peripheral fatty acid metabolism. In the backward stepwise multiple regression carried out in the HF group age, acetylcarnitine intensity and serum uric acid concentration were negatively associated with a negative percent of deficit in lyso-PC 14:0, 18:0, 18:2 and lyso-PE 18:1 while serum carnitine intensity, renal function, total cholesterol, LDL and HDL level presented positive association with percent of deficit in lyso-PC 14:0, 18:0, 20:3 and lyso-PE 18:1.

Untargeted metabolomics approach revealed significant disturbances in phospholipids metabolism among chronic heart failure patients. Greater reduction in PLs was identified among HF patients with more advanced disease: older, with more severe metabolic dysregulation, enhanced catabolic state, impaired renal function, reduced oxidative muscles metabolism and decreased exercise capacity. Results of our study suggest that the dysregulation in phospholipids metabolism may play an important role in HF pathophysiology. However, further research is needed to fully elucidate the exact metabolic mechanism (activated immune system, impaired energy metabolism, altered choline metabolism or a role of gut microbiota) responsible for the dysregulation in PLs metabolism in patients with chronic HF.