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Review

Metabolomics — A wide-open door to personalized treatment in chronic heart failure?

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ABSTRACT

Heart failure (HF) is a complex syndrome representing a final stage of various cardiovascular diseases. Despite significant improvement in the diagnosis and treatment (e.g. ACE-inhibitors, β-blockers, aldosterone antagonists, cardiac resynchronization therapy) of the disease, prognosis of optimally treated patients remains very serious and HF mortality is still unacceptably high. Therefore there is a strong need for further exploration of novel analytical methods, predictive and prognostic biomarkers and more personalized treatment. The metabolism of the failing heart being significantly impaired from its baseline state may be a future target not only for biomarker discovery but also for the pharmacologic intervention. However, an assessment of a particular, isolated metabolite or protein cannot be fully informative and makes a correct interpretation difficult. On the other hand, metabolites profile analysis may greatly assist investigator in an interpretation of the altered pathway dynamics, especially when combined with other lines of evidence (e.g. metabolites from the same pathway, transcriptomics, proteomics). Despite many prior studies on metabolism, the knowledge of peripheral and cardiac pathophysiological mechanisms responsible for the metabolic imbalance and progression of the disease is still insufficient. Metabolomics enabling comprehensive characterization of low molecular weight metabolites (e.g. lipids, sugars, organic acids, amino acids) that reflects the complete metabolic phenotype seems to be the key for further potential improvement in HF treatment (diet-based or biochemical-based). Will this -omics technique one day open a door to easy patients identification before they have a heart failure onset or its decompensation?

1. Background

Heart failure (HF) is a complex syndrome representing a final stage of various cardiovascular diseases. Recent progress in the pharmacological and invasive treatment of patients with coronary artery disease has led to a significant life prolongation. This occurred at the cost of more patients living with severe impairment of heart function contributing to increased occurrence of the heart failure in the older age. In the developed countries, the incidence of HF in the population of over 70 years old is higher than 10% [1]. Despite significant improvement in the diagnosis and treatment (e.g. ACE-inhibitors, β-blockers, aldosterone antagonists, cardiac resynchronization therapy) of the disease, prognosis of optimally treated patients remains very serious and HF mortality is still unacceptably high [2,3]. It may in part be due to the insufficient knowledge of the pathophysiological mechanisms leading to the progression of the disease. In fact, several already defined different clinical models such as neurohormonal, cardiorenal and hemodynamic are useful in describing changes (e.g. neurohormonal activation, multiorgan dysfunction) associated with the clinical syndrome of the HF. Nevertheless, none of them fully explains the pathophysiological mechanism responsible for the development and progression of the disease. Therefore there is a strong need for further exploration of novel analytical methods, predictive and prognostic biomarkers. This may allow early diagnosis of the disease as well as identification of individuals at risk of rapid progression of HF. Moreover, an

Abbreviations: ACLI, acute cardiogenic liver injury; ADP, adenosine diphosphate; ATP, adenosine triphosphate; BNP, B-type natriuretic protein; CE, capillary electrophoresis; CH, cardiac hepathopathy; CK, creatine kinase; CPT-1, carnitine palmitoyltransferase-1; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; DHEA-S, dehydroepiandrosterone sulfate; $FABP_{pm}$, plasma membrane-associated fatty acid-binding protein; FAO, fatty acid oxidation; FAs, fatty acids; FAT/CD36, fatty acid translocase; FATPs-1, fatty acid transporter proteins 1; FATPs-6, fatty acid transporter proteins 6; G-6-P, glucose-6-phosphate; GC, gas chromatography; GLP-1, glucagone-like peptide-1; GLUTs, transmembrane glucose transporters; HF, heart failure; $H\text{-}FABP_c$, heart-type cytoplasmic fatty acid-binding protein; IR, insulin resistance; LC, liquid chromatography; LC-QQQ, liquid chromatography triple quadrupole; LVEF, left ventricle ejection fraction; MRM, multiple reaction monitoring; MS, mass spectrometry; NADH, nicotinamide adenine dinucleotide; NMR, nuclear magnetic resonance; NT-proBNP, N-terminal proBNP; PCr, phosphocreatine; PPARs, peroxisome proliferator-activated receptors; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SIM, single reaction monitoring.

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analytical tool that enables identification of those who can benefit from particular types of therapy (e.g. cardiac resynchronization therapy — CRT) may allow more personalized treatment.

The metabolism of the failing heart is significantly impaired from its baseline state. Hence, it may be a future target not only for biomarker discovery but also for the pharmacologic intervention. Nevertheless, analytical methods that target a particular, isolated metabolite or protein cannot provide fully informative results and make their correct interpretation difficult. An assessment of an overall metabolite profile may greatly assist investigator in an interpretation of the altered pathway dynamics, especially when combined with other lines of evidence (e.g. metabolites from the same pathway, transcriptomics, proteomics). Metabolomics enables comprehensive characterization of low molecular weight metabolites (e.g. lipids, sugars, organic acids, amino acids) reflecting the complete metabolic phenotype. This -omics technique has already been used for identification of markers associated with various pathologies such as myocardial ischemia [4–6], cardiogenic shock [7], atherosclerosis or future cardiovascular events [8–10], diabetes mellitus [11], atrial fibrillation [12,13] and chemotherapy-induced cardiotoxicity [14]. The number of studies on application of metabolomics in heart failure assessment is rapidly growing, however the heterogeneity in methodology (e.g.: various body fluids such as urine, serum, plasma; different metabolomics techniques; inclusion of patients in various stages of HF) still makes their results difficult to compare. Will the metabolomics one day open a door to easy patients identification before they have a heart failure onset or its decompensation?

This review describes alterations in cardiac energetics and in metabolism of other organs in HF patients. Current metabolomics techniques, their possible application and limitations are also discussed.

2. Cardiac energetics — an engine out of fuel

Glucose and lactates are the main substrates for energy production in prenatal heart. In the postnatal period, under normal conditions the heart is a versatile user of metabolic substrates with the vast majority of adenosine triphosphate (ATP) produced by fatty acid oxidation (FAO) [15]. The amount of the energy used by the healthy working heart exceeds significantly energy consumption by other organs and is associated with decomposition of approximately 6 kg of the ATP. Hence, even the smallest changes in the ATP production rate make huge impact. There are three key regulatory stages of the heart energy metabolism (substrate supply, oxidation with ATP production, ATP transfer to cytoplasm where it is consumed by the myofibrils). Metabolic perturbations observed in the course of the heart failure concern every step of the cardiac energy metabolism. In the healthy adult heart, substrate utilization may vary depending on the myocardial energy needs and the availability of a particular substrate (e.g. during the physical activity, reduced availability of oxygen) [16]. In addition, metabolism of one substrate can inhibit utilization of an alternative one, as it has been previously described in the glucose–fatty acid cycle [17]. Though, failing heart gradually loses its ability for flexible substrate selection and under the chronic hemodynamic stress switches metabolic pathways from fatty acids to carbohydrates [18]. While in the early stages of the disease both glucose and FA metabolism is enhanced, further HF progression leads to continued increase in glucose utilization and simultaneous reduction in free FA metabolism. End-stage HF is characterized by the depletion of energy resources due to the decreased metabolism of both main myocardial fuels (Fig. 1) [40]. To date, abnormalities in several processes of fatty acid metabolism have been identified in patients with heart failure. This includes selection [19], transport [20–21], oxidation [20–22] and respiratory chain activity [20–21,23–26]. Free FAs cross the lipid bilayer in a passive manner via flip-flop or by using transport proteins (i.e.: fatty acid translocase — FAT/CD36, the plasma membrane-associated fatty acid-binding protein — $FABP_{pm}$, fatty acid transporter proteins 1 and 6 — FATPs1/6) [27]. After entering the cytoplasm, free FAs are either bound by the heart-type cytoplasmic fatty acid-binding protein ($H\text{-}FABP_c$) or are converted into acyl-CoA by acyl-CoA synthetase. Further, acyl-CoA can be either esterified and stored in lipid droplets or can be transported to mitochondria [27]. Glucose transport into myocytes is regulated by the specific transmembrane glucose transporters (GLUTs) localized in the sarcolemma [28]. Expression levels of both GLUT-1 (the main fetal insulin-independent

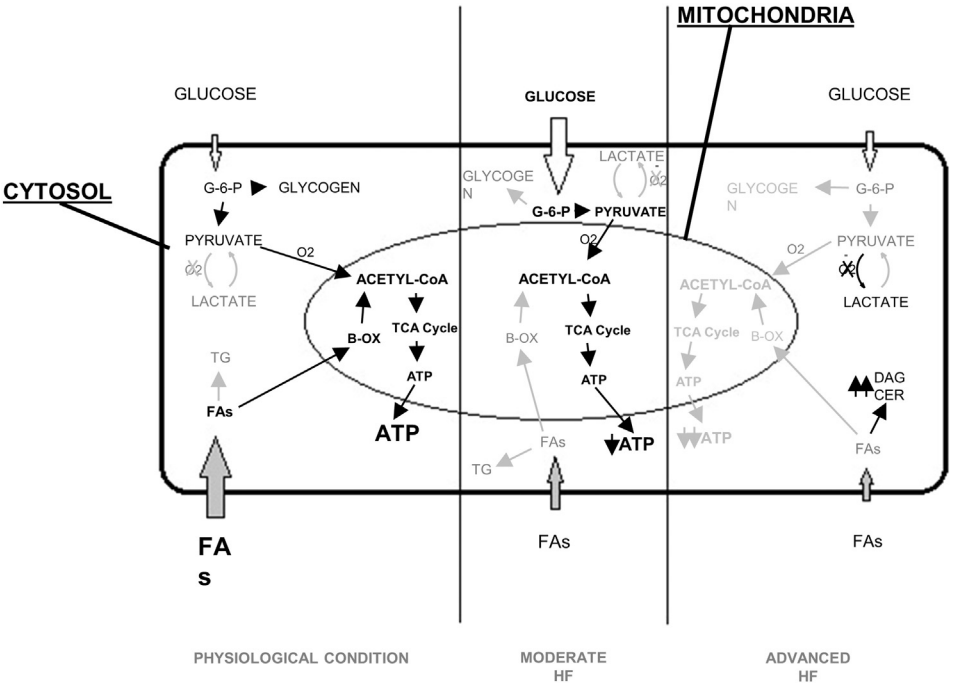

Fig. 1. The metabolism of two main myocardial fuels (FAs — fatty acids, glucose) in physiological condition and in the course of heart failure (HF) development. To simplify the figure enzymes are not included and reactions despite being in the vast majority bidirectional are presented as unidirectional. G-6-P — glucose 6-phosphate; O2 — oxygen; TG — triglycerides; β-OX — beta-oxidation; TCA cycle — citric acid cycle (Krebs cycle); ATP — adenosine triphosphate; DAG — diacylglycerol; CER — ceramides.