

# Dynamics of Metabolomics in Patients of Heart Failure

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## Abstract

Heart failure remains a leading cause of death in patients with established cardiovascular disease. The biomarkers reflecting staging and evolution of HF appear to be promised tool to risk stratification and target-based therapy. In the editorial adaptive metabolic transitions of HF with reduced and preserved left ventricular ejection fraction are considered. It has discussed the role of metabolites in the regulating function of the failing heart. The use of metabolites, i.e. polyamines, putrescine, spermidine, spermine, ornithine decarboxylase, and acylcarnitine, in patients with HF is considered. Future directions regarding molecular biology techniques, which substantially contribute to assay of metabolic profile in HF patients aimed improving clinical outcomes, response to the individualized therapy, are emphasized.

Keywords:

Heart failure; Metabolism; Biomarkers; Clinical outcomes; Metabolomics; Proteomics

## Discussion

Although in the developed countries the incidence of newly chronic heart failure (HF) with reduced left ventricular ejection fraction (HFrEF) have now decreased, during the past several decades newly cases of HF with preserved left ventricular ejection fraction (HEpEF) or mid-ranged left ventricular ejection fraction have steadily exhibited a rise [1,2]. Frequent co-existing clinical conditions, i.e. diabetes, chronic pulmonary disease, hypertension, left ventricular hypertrophy, and aging are the most important factors contributing to development of different phenotypes of HF [3]. Current clinical guidelines regarding treatment and prevention of HF are recommended to widely use biomarkers reflecting various faces of pathophysiology of HF [4,5]. Natriuretic peptides (NPs), soluble ST2, galectin-3, and cardiac troponins are validated to stratify the HF patients at risk of death, admission/re-admission, advance of HF, cardiovascular events [6-8]. Therefore, NPs are not only diagnostic tool for determination in symptomatic

HFpEF/HFrEF, but they are essential for target therapy of HF [5,7]. Galectin-3 is predictive biomarker in risk stratification among HFpEF/HFrEF patients and general population individuals at higher risk of HF development [9,10]. However, among younger patients of both sexes, adult female, older subjects there were not enough evidence with respect to improving HF-related outcomes, when traditionally used biomarkers were implemented [11,12]. Yet, the increased biological variability and extended diagnostic "grey zone" for single and serial measured biomarkers (i.e. NPs, galectin-3) make to discover more diagnostically accurate and prognostic ally powerful biomarkers and their combinations. In this context, metabolic disturbance, which is remarkable in patients with different phenotypes of HF, might demonstrate powerful diagnostic and predictive values facilitating optionally used clinical-based and biomarkers-related predictive scores [13,14].

It is suggested that phenotype response of altered myocardium is under control of epigenetic mechanisms and relates to several pathophysiological pathways affected transcriptomics and metabolomics [15,16]. Probably, adaptive metabolic transitions of HF could associate with staging and severity of HF, predominantly HFrEF, aging, and co-existing comorbidities including obesity, diabetes, and hypertension. Whether the metabolomic signature might be unique chemical fingerprints for HFrEF and HFpEF is not fully clear and requires be checking and broadly investigating. Finally, metabolites could provide important information for the identification of HF at early stage and help to understand HF progression [17].

Recent basic and clinical studies are investigated the broad spectrum of various small-to-moderate molecule metabolites characterized the underlying mechanisms of failing heart development and its comorbidities. The biogenic amines, i.e. polyamines, putrescine, spermidine and spermine, are involved in many cellular processes, including apoptosis, and may regular catecholamine and lipid toxicity [18]. There is evidence regarding involvement of polyamines in apoptosis of cardiac myoblasts and cardiac hypertrophy [19]. Ornithine decarboxylase and acylcarnitine play a pivotal role in cardiac growth, hypertrophy and arrhythmias [20].

value similar to B-type NP in patients with severe chronic HF. Additionally, another metabolite panel constructed from the asymmetric methylarginine/arginine ratio, butyrylcarnitine, spermidine, and the total amount of essential amino acids, provided sufficient prognostic values independent of NPs and traditional HF-related risk factors. Authors concluded that the prognostic value of the metabolite panel was better than that of NPs in severe HF individuals. Nemutlu et al (2015) [21] found altered metabolic profile in plasma (i.e., higher isoleucine, phenylalanine, leucine, glucose, and valine levels and lower glutamate levels) among patients with advance HF with ventricular dyssynchrony. After use of cardiac resynchronization therapy (CRT) harmonization of myocardial energy substrate metabolism was determined. Thus, metabolomic profile could consider a potential biomarker for predicting CRT outcome in HF patients. Ahmad et al (2016)

[22] have analyzed perturbations in energy homeostasis and metabolism using a signature of 60 circulating metabolites in HFREF patients. Authors have found that the long-chain acylcarnitine metabolite levels were independently associated with adverse HF-related clinical outcomes and decreased after long-term mechanical circulatory support device. Interestingly, that the elevated myocardial energy expenditure in HFREF was associated with significant changes in serum metabolomics profiles, especially the concentration of 3-hydroxybutyrate, acetone and succinate [23]. Moreover, these three metabolites have found an independent association with myocardial energy expenditure beyond administration of angiotensin converting enzyme inhibitor, beta-receptor blockers, diuretics and statins.

Taken together these findings allow to note that signature of metabolites rather than a single molecule elucidate metabolic perturbations in HF and may implement a diagnostic and/or predictive tool in HFREF individuals across evolution of failing heart. Whether combining proteomics and metabolomics could correspond to identify HF at risk of HF-related complications is not fully clear [24]. In future, molecular biology techniques, which substantially contribute to assay of metabolic profile in samples received from blood, saliva, urine, etc. on real time-dependend manner, might considered a diagnostic tool to improve method of target therapy of HF [25].

In conclusion, diagnostic value of metabolic profile in HFREF/ HFpEF patients requires more investigations, while its harmonization probably associates with improving clinical status and HF-related outcomes. The signature of metabolites might provide better predictive value compared with conventional biomarkers in HFREF patients, whereas in HFpEF individuals there is limiting evidence. Using metabolomics assay in HF individuals to individualize treatment strategy is promised approach, while its efficacy is not yet defined and requires a scrutiny in the future.

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