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Chapter 9

Application of Metabolomics for the Diagnosis and Traditional Chinese Medicine Syndrome Differentiation of Chronic Heart Failure

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http://dx.doi.org/10.5772/66209

Abstract

Chronic heart failure (CHF) was characterized by the failure of enough blood supply from the heart to meet the body's metabolic demands, and the prevalence of CHF continuously increases globally. The personalized diagnosis of Traditional Chinese Medicine (TCM) classifies CHF into several different syndrome types, and integrating Western and TCM to treat CHF has proved a validated therapeutic approach. Over the last few years, there has been a rapidly growing number of metabolomics applications aimed at finding biomarkers that could assist diagnosis, provide therapy guidance, and evaluate response to therapy for individualized intervention of CHF. Thus, in this review, particular attention will be paid to the past successes in applications of state-of-the-art technology on metabolomics to contribute to biomarker discovery in CHF research.

Keywords: metabolomics, chronic heart failure, Chinese Medicine

1. Introduction

Chronic heart failure (CHF), a progressive clinical syndrome characterized by the inability of the heart to adequately pump blood to meet metabolic demands of the body, represents the final common ground of pathogenesis wherein various causes of heart damage converge [1].

Despite a substantial improvement in the survival rate after the onset of CHF due to increasing use of pharmacological interventions, mortality of patients suffering from CHF remains high. Since it has been well recognized that the incidence and prevalence of CHF are expected to further increase with the aging of the population, better strategy for the prevention and treatment of CHF patients is still needed.

1.1. Epidemiology of CHF

CHF, in recent years, has been a major cause of morbidity and mortality in the general population [2]. Both the increasing age of the population and success in the treatment of patients with acute myocardial infarction raise the prevalence and thus the economic expenditures of chronic heart failure [3]. Heart failure is not only a common, costly, disabling, and potentially fatal condition but also the leading cause of hospitalization in people older than 65 [4]. In developing countries, 2–3% of the population suffers from heart failure, but in people from 70 to 80 years old, it occurs in 20–30% [5]. In developed countries, around 2% of adults suffer from heart failure, but in people older than 65, this increases to 6–10% [6].

1.2. Personalized intervention of CHF based on Traditional Chinese Medicine (TCM) syndrome

With progress being made in bioinformatics and medical science, the view on health and disease in Western life sciences has shifted from standard protocol-based disease management to personalized medicine [7]. Based on personalized health and systematically diagnostic principles, Traditional Chinese Medicine (TCM) has proved effective to restore the self-regulatory ability of the human system by thousands of years in clinic. And using integrating TCM and Western medicine to treat CHF has been reported to enhance heart function and reduce related clinical symptoms, including expiratory dyspnea and chronic fatigue, and subsequently improve echocardiographic measures, 6-min walking distance test, and patients' quality of life [8]. TCM physicians also pay more attention to the overall maladjustments of functional status called "syndrome type" [9]. It is not simply an assemblage of diseases' signs and symptoms but also a functional status caused by the reaction to or interaction with environmental changes and pathogenic factors [10]. In other words, the essence of TCM "syndrome type" is disturbance in biological metabolism networks, the changes in concentration and relative proportions of metabolomic biomarkers resulting from the imbalance of the human system. For example, yin deficiency syndrome of CHF patients is described as low fever, night sweats, afternoon zygomaticus red, dysphoria (fever) in chest palms soles, dry mouth and throat, red tongue with little coating, and thready rapid pulse according to the Clinical Terminology of Traditional Chinese Medical Diagnosis and Treatment—Syndromes, and Yang deficiency syndrome of CHF is a cluster of symptoms including an aversion to coldness, dispirited feelings and lack of motivation, diarrhea before dawn, shortness of breath, frequent urination, edema, and liability to catch cold. Therefore, TCM syndrome, also defined as TCM pattern, is the essence of diagnosis and treatment in TCM.

http://dx.doi.org/10.5772/66209

2. Bringing metabolomics into the forefront of CHF research

The metabolome is the final downstream product of transcription and translation and is thus closest to the phenotype [11]. Dynamics of primary metabolism operate in timescales of seconds. These two characteristics allow the metabolome to be a sensitive and rapid measure of the system phenotype. Metabolomics were first defined in 1998 [12, 13]. Progress has been made in methodological technologies that have lead to the discovery of metabolomic biomarkers and greater knowledge regarding disease mechanism from that time. From the 1960s, applications of mass spectrometry (MS) [14] and nuclear magnetic resonance spectroscopy [15, 16] drove the first holistic studies of mammalian biofluids to be conducted. In the past years, the development of technology has given impetus to metabolomics to its current status. More than 13,000 studies searched in PubMed Database have proved metabolomics a routinely applied tool nowadays. However, metabolomics is still the younger and smaller sibling of proteomics, transcriptomics, and genomics. Metabolite profiles can provide a fingerprint of metabolic changes that characterize the mechanism of CHF, a progressive clinical syndrome, and also highlight the potential of metabolomic analysis in the evaluation of disease condition.

Metabolomics, as an important component of systematical biology, can be used to perform dynamic studies on noninjured tissues and organs in vivo and in vitro using noninvasive approaches under nearly physiological conditions. Therefore, metabolomic detection and analysis of biological samples may contribute to understand the biochemical changes associated with the progression of diseases. And identification of disease-associated metabolic biomarkers could allow early diagnosis of disease and establishment of predictive diagnostic systems. It is reported that metabolomics gives itself unparalleled advantage to the most common cardiovascular condition encountered in clinical practices, heart failure [17]. Metabolomics has also showed significant potential in TCM studies in recent years. And several studies [18, 19] combining metabolomic techniques and TCM syndrome types have demonstrated fingerprints of metabolic changes that characterize Western Medicine-diagnosed diseases, which highlighted the potential of metabolomics in the evaluation of disease condition and TCM-guided personalized treatment.

2.1. General procedures in which metabolomics can be used for diagnosis and biomarker discovery

Metabolomics operates with a workflow [20, 21] starting from a biological question and experiment, proceeding through sample collection and preparation, analytical experiment(s) to acquire data, data preprocessing and analysis followed by biological interpretation. The metabolomics experimental workflow involves the design of biological and analytical experiments, sample preparation, data acquisition, data preprocessing and analysis and data interpretation. This workflow leads to biological interpretation and reasoning, as shown in **Figure 1**.

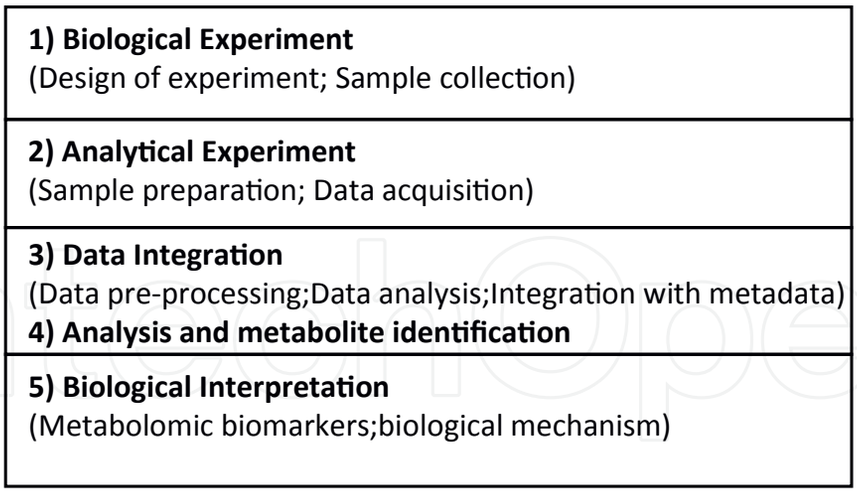

Figure 1. The general workflow of metabolomic experiment.

Specifically, analytes in a metabolomic sample comprise a highly complex mixture. Mass spectrometry (MS) is used to identify and to quantify metabolites after optional separation by liquid chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), nuclear magnetic resonance (NMR) spectroscopy, and capillary electrophoresis (CE). The raw data usually consist of measurements performed on subjects under various conditions. These measurements may be digitized spectra, or a list of metabolite levels. The software, called XCMS, is one of the most widely cited mass spectrometry-based metabolomics software programs in scientific literature. Prior to multivariate data analysis, statistical analyses are performed using SIMCA-P+12 software (Umetrics, Umea, Sweden) as variables and then mean-centered and pareto-scaled. Principal component analysis (PCA) and orthogonal partial least-squares discriminant analysis (OPLS-DA) are commonly used for the processed data. Score and loading plots are calculated to demonstrate discriminatory metabolites for each group; clustering of samples with similar metabolic fingerprints can be detected. This clustering can elucidate patterns and assist in the determination of disease biomarkers.

Two generalized experimental strategies are applied, metabolic profiling (or metabolomics) and metabolite-targeted analysis. Metabolic profiling allows comprehensive phenotyping of genetically or environmentally modified systems. The study is devised so as to acquire data on a large scale of metabolites (100–1000s) followed by interrogation of these data to figure out biological differences. The design of metabolomic experiments is of great importance here as it becomes easier to introduce confounding factors that are not recognized during data analysis and which can falsify biological conclusions [22].

2.2. Advances in metabolomics techniques and related statistical methods

Without knowing which metabolites are of specific biological interest, powerful analytical methods are used to illustrate thousands of metabolites reproducibly in a single sample. Relative alterations in metabolite concentrations are researched, and at this stage, the absolute concentrations of metabolites are not generally identified. With the goal to figure out all

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metabolites, this is currently not technologically realized. A platform of sample preparation and analytical methods is applied to acquire good coverage of identified metabolites (e.g., give reference to the Husermet project where LC-MS, GC-MS, and NMR spectroscopy have all been used; www.husermet.org). The application of univariate and multivariate analysis tools [23–25] was performed to process data. These discovery-phase researches and hypothesis-generating or inductive studies [26], sometimes by the non-cognoscenti as a "fishing expedition," aim to detect new biological and metabolomic markers. Moreover, another strategy, driven from known biology where a limited number of metabolites (generally less than 20) are known to be biologically relevant before the biological experiment, is conducted, and accurate quantification of distinguished metabolites is analyzed in a designed approach. Under the remit of traditional analytical chemistry and biochemical assays commonly found in clinical laboratories, this strategy has been applied for decades.

3. Biomarkers and metabolomics studies on CHF

In studies of human beings, metabolomics has been applied to define biomarkers related to prognosis or diagnosis of a disease or drug toxicity/efficacy, and it is hoped to provide greater pathophysiological understanding of disease or therapeutic toxicity/efficacy by these studies [27]. Coupling bioinformatics and biostatistics with metabolomic technology platforms permits the identification and quantification of molecules to characterize the whole organism's response to diseases [28]. Studies have demonstrated that metabolomics lends itself ideally to the most common cardiovascular condition encountered in clinical practices, heart failure [29]. Serum metabolites collected from 52 patients developed with CHF and 57 controls were analyzed and 38 peaks illustrated significant differences between patients and controls. As the current gold-standard biomarker brain natriuretic peptide (BNP), two metabolites of pseudouridine including a modified nucleotide present in tRNA and rRNA, a marker of cell turnover, and the tricarboxylic acid cycle intermediate 2-oxoglutarate were at least as diagnostic metabolic biomarkers of heart failure [30]. Moreover, 2-hydroxy, 2-methylpropanoic acid, erythritol, and 2, 4, 6-trihydroxypyrimidine were also good discriminators for cases and controls observed. We identified metabolites from early experiments, also biomarkers in the future, and will need to lay a foundation for larger, prospective, externally validated researches in clinical studies. Our study used to apply a metabolomics approach to plasma obtained directly from patients in order to assess its accuracy and reliability in diagnosing CHF, which showed better performance in terms of both specificity and sensitivity. It should be noted that the heart is known to consume a diverse set of fuel substrates, including lactate, glucose, amino acids, ketones, and particularly free fatty acids (FFAs). The metabolites include energy metabolism-related molecules, lipid/protein complexes, and amino acids. Plasma samples from 39 CHF patients and 15 controls were analyzed by NMR spectroscopy. After processing the data, PCA and OPLS-DA were performed. The statistical model revealed good explained variance and predictability, and the diagnostic performance assessed by leave-one-out analysis exhibited 92.31% sensitivity and 86.67% specificity. The OPLS-DA score plots of spectra revealed good separation between case and control on the level of metabolites, and multiple

biochemical changes indicated hyperlipidemia, alteration of energy metabolism, and other potential biological mechanisms underlying CHF. It was concluded that the NMR-based metabolomics approach demonstrated good performance to identify diagnostic plasma markers and provided new insights into metabolic process related to CHF.

It has become well recognized that alteration in energy metabolites is of great importance in chronic heart failure in recent years. Impairment in extraction of a wide range of metabolites, probably pointing to severe energy deficiency, always leads to cardiac dysfunction in CHF patients. Moreover, higher level of lactate and decreased glucose in plasma metabolites seem to aggravate the impairment of energetic pathway in patients with CHF. A few metabolites relevant only in distinguishing CHF patients from healthy controls could be associated with prolonged exertion. Therefore, we observed increased lactate during anaerobic exercise. When stores of glucose are low and concentration of oxaloacetate has been exhausted, acetone is generated accordingly. Furthermore, alanine is expected to rise resulting from gluconeogenesis when lactate is produced [31]. A rise in creatine, phosphorylated to phosphocreatine in muscle, may indicate a physiological state of energy depletion. Besides, glycolate is of great importance in energy generation by mitochondria. Pyruvate stem from glycolysis is diverted away from the pyruvate dehydrogenase and toward the lactate dehydrogenase reaction, which contributes to the increase in lactate. A rise in acetyl-CoA may facilitate the inhibition of pyruvate dehydrogenase, which continues to be stemmed from fatty acid oxidation; however, it accumulates on the account of lowered trichloroacetic acid (TCA) cycle flux. Stress on energy metabolism can also affect metabolic area in CHF patients. 3-Hydroxybutyrate, 2-hydroxyisobutyrate, and 3-methyladipate had proved significant in glucose and lipid metabolism by Lin's study [32]. Glycoprotein and carnitine are reported in oxidative metabolism in mitochondrial and hypoxemic stress [33]. These results suggested oxidative fuel decrease and a greater reliance on anaerobic metabolism of glucose for energy production in the plasma of CHF patients.

In CHF patients, increased low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL) were observed to be relative to lipolysis as a backup mechanism for energy generation. Previous proteomic analysis of left-atrial cardiomyocyte and tissue samples from the congestive heart failure model also found significant alterations in apolipoprotein levels [34]. As apolipoproteins play a significant role in lipid metabolism, the alterations in apolipoprotein concentrations indicate that lipid metabolic dysregulation may be relative to CHD. Other studies have shown a close relationship between CHF and lipid regulation, which may account for the high comorbidity between metabolic syndrome and CHF [35]. Along these lines, previous study examining FFA extraction in myocardial ischemia patients also has found decreased FFA extraction and oxidation [36]. Choline and its derivatives represent important constituents in phospholipid metabolism of cell membranes and have been previously identified as markers of cellular proliferation. To summarize, CHF patients have limited myocardial metabolic reserve and flexibility, which verify a preliminary hypothesis of association between lipid metabolic disorder and CHF.

The change of the TCA cycle may also be a metabolic marker in CHF patients. Impaired TCA cycle flux, derived from the catabolism of glucose and amino acids, appears to occur in part

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through limiting levels of anaplerotic substrates [37]. The fall in glutamate/glutamine uptake was observed in CHF patients because they would normally be transfinite to form the anaplerotic substrate α-ketoglutarate. An increase in alanine release was also noted. The net production of alanine likely occurs via transamination of pyruvate, with glutamate as the nitrogen donor in the alanine transaminase reaction. In this period, this metabolic signature is consistent with impaired glucose oxidation resulted in the diversion of pyruvate away from the TCA cycle and into alanine transaminase reactions. Some scholars hypothesize that CHF activates proteolysis of skeletal muscle and enhances branched amino acid oxidation, as was described in inflammatory states [38]. Besides that, increased proline had been reported to play a role in coronary atherosclerosis diseases [39]. In view of these studies, the heart's ability to maintain homeostasis via glycogeolysis, neoglucogenesis and ketogenesis is compromised with CHF, as well as altering the amino acids.

4. Diagnostic power of metabolomics in TCM syndromes of CHF

Despite advances in the drug treatment strategy for CHF, the number of deaths resulting from this condition continues to rise [40]. TCM pays special attention to the integrity and holism of the human body and its interrelationship with nature. Based on different symptoms and signs, TCM adheres to the basic principle to treat the same disease by different methods and different diseases by one method and emphasizes personalized treatment, which truly indicates the essence of TCM intervention [41]. Therefore, treatment based on syndrome differentiation is the core of TCM therapy or CHF. From the perspective of TCM, CHF may occur in all differentiation types, including qi deficiency and blood stasis, yang deficiency and water retention, yin deficiency, and so on. Many Chinese herbs have demonstrated safety and efficacy in the management of chronic heart failure in either animal models or humans [42, 43]. In addition, modern biologic research has entered an era of integrating various research technologies and methods to tackle difficult biological problems at biomolecular level as a whole, which is exemplified by studies in the new scientific fields of metabolomics. It is therefore crucial to investigate the potential correlation between TCM syndrome type and metabolites to develop novel therapeutic approaches for better treatment of CHF.

4.1. Qi deficiency and blood stasis syndrome

Based on TCM, we classified CHF patients into several syndromes. We investigated plasma metabolites of CHF patients with qi deficiency and blood stasis syndrome to illuminate new approaches to the diagnosis and identify metabolic signatures of TCM syndromes in CHF. Combining plasma metabolomics with TCM syndrome-type diagnosis showed the distinguished metabolites of CHF patients with qi deficiency and blood stasis syndrome, including energy metabolites (glucose, lactate, and glycoprotein), lipid/protein complexes [HDL, LDL/very low-density lipoprotein (VLDL)], and amino acids (alanine, glutamate, valine, glycine, proline, and carnitine). Therefore, this metabolomic method may demonstrate potential in understanding of TCM syndromes of CHF. It is indisputable that there are limitations to each study with any other new diagnostic approaches. Here, the effects of other confounding factors

on the metabolic profiles, though, can be analyzed by further studies with large cohort required to validate this method. For plasma samples representing the effects of metabolism in different organs, it is also difficult to assign a metabolic fingerprint to specific metabolic processes [44]. However, it should be noted that the altered metabolites are reflected in CHF patients with certain TCM syndrome, which can be harnessed as markers of diseases.

Qi deficiency and blood stasis syndrome, as a major syndrome among CHF patients, show a distinct signature of altered metabolism, which includes increased level of lactate, gly-protein, low-density lipoprotein (LDL)/very low-density lipoprotein (VLDL), and lower levels of glucose, valine, proline, alanine, and carnitine. And glycoprotein is closely associated with the physiology and pathology of cells' growth and can affect human metabolic energy supply and cellular immunity [45]. Furthermore, increased level of LDL and VLDL was observed in CHF patients with qi deficiency and blood stasis syndrome, which were the most prominent factors differentiating from controls. This metabolomics profile could be associated with lipolysis as a backup mechanism for energy utilization, for apolipoproteins are of great weight in lipid metabolism. Meanwhile, the plasma levels of well-known essential and nonessential amino acids (such as alanine and valine) decreased in the CHF patients with qi deficiency and blood stasis syndrome, breaking the internal equilibrium of the body gradually. This is in line with Yan's research; a metabolomics study on the rat model of myocardial ischemia with this syndrome showed that increased inositol and decreased valine, glycine, and serine were closely associated with energy metabolism and oxidative stress response [46]. Besides that, carnitine, an important substance involved in fat metabolism and energy supply, reduced dramatically in these patients. Studies have confirmed that L-carnitine can increase the uptake of free fatty acids (FAA), which will make use of glucose as oxidative fuel in certain circumstances [47]. If carnitine was insufficient, the oxidation process in mitochondria will be affected, which leads to the imbalance of cell metabolism and heart diseases. Tricarboxylic acid cycle, carbohydrates, proteins, and fats would involve in the above metabolic processes, indicating a complicated metabolic disorder in CHF patients with qi deficiency and blood stasis syndrome. Therefore, this metabolomic method may demonstrate potential in understanding of qi deficiency and blood stasis syndrome of CHF. It is indisputable that there are limitations to each new diagnostic approach. The effects of other confounding factors on the metabolic profiles, though, can be analyzed by further studies with large cohort required to validate this method [47]. For plasma samples representing the effects of metabolism in different organs, it is also difficult to assign a metabolic fingerprint to specific metabolic processes. However, it should be noted that these altered metabolites are at least partly reflected in CHF patients with qi deficiency and blood stasis syndrome, which can be harnessed as markers of diseases for personalized treatment based on TCM. Further mechanistic studies regarding this issue are warranted.

4.2. Yang deficiency and water retention syndrome

Yang deficiency and water retention patients were observed to show higher levels of lactate, gly-protein, pyruvic acid, alanine, glutamate, and lower levels of glucose, low-density lipoprotein (LDL)/very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL).

Based on TCM theory, yang deficiency is associated with signs of chronic, weak, hypofunction, hypometabolism, degenerative symptoms, and extremely common to be observed in late or severe stage of many diseases [48]. The metabolism pattern in CHF patients with yang deficiency and water retention syndrome demonstrated the decrease in glucose metabolism and the increase in lactate, alanine, and pyruvate, suggesting that the disorder of carbohydrate and energy metabolism in patients is more serious. There might be enhanced endogenous glucose production from gluconeogenesis and pyruvic acid change may indicate increased hepatic gluconeogenesis to provide extra pyruvate as a substrate for glucose [49]. That is why syndrome typically occurs in patients with chronic heart failure at stage III and stage IV. Moreover, increased glycoprotein indicates immune defects in the patients [50], while the generally lower lipoprotein levels including LDL/VLDL and HDL also suggest the insufficient absorption and utilization of protein in this phase. And higher excretion of measured metabolites (glutamate and alanine) could indicate that they might have more potential disturbance of renal function, and resultant missed metabolites that are necessary for carbohydrate and energy metabolism [51]. Previous study [52] investigated the urinary metabolites of syndrome in patients with chronic kidney disease and revealed that the key distinguished metabolites differed between yang deficiency and water retention syndrome and control group including alanine, diethylamine, proline, and so on. As essential substance in cellular activities, the deficiency will affect energy supply in all aspects of human body. Finally, these alterations are likely important contributing factors to the altered metabolite profiling of CHF patients with yang deficiency and water retention syndrome.

5. Conclusions and future perspectives

The future goals for metabolomics are the validation of existing biomarkers in terms of mechanism and translation to man, together with a focus on characterizing the individual health care. So far, metabolomics may be of special clinical relevance for the diagnosis of syndromes of CHF and uncovering metabolomic pathway and prognosis in some extent, which could lead to a better understanding and improvement of personalized interventions for CHF. Metabolomics has also shown great advantage to discover possible early biomarkers for the development of CHF and assess progression during treatment, which can aid the discovery of prognostic indicators of outcome and disease response to personalized therapy.

Acknowledgements

This work was supported by the National Department Public Benefit Research Foundation of China under grant no. 200807007 and the National Natural Science Foundation of China under grant no. 81302914.

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