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Evaluation of Chinese medicine on heart failure based on NMR metabolomics

Jing Chen [a], Bin Li [a], Huihui Zhao [a], Zhongfeng Li [b], Juan Wang [a], Dong Deng [a], Wei Wang [a,*]

[a] *Beijing University of Chinese Medicine, Beijing 100029, China*
[b] *Capital Normal University, Beijing 100048, China*

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Abstract *Objective:* To evaluate the efficacy of traditional Chinese herbs on heart failure (HF) using nuclear magnetic resonance (NMR) metabolomics.
Methods: Plasma metabolomics was conducted on both patients with HF and healthy controls. The partial least squares model was applied to determine potential metabolic markers and related metabolic pathways of the disease. HF patients with the traditional Chinese syndrome pattern of *qi* deficiency and blood stasis were divided into two groups, and treated, respectively, with conventional medicine and a combination of conventional and Chinese herbs, aimed at tonifying *qi* and activating blood. Healthy participants served as a control group for comparison.
Results and conclusion: Both conventional and herbal treatments appear to regulate disorders of amino acid and glucose metabolism. Combined treatment appears to be more comprehensive, indicating that herbal and conventional medicines exert their effects through different mechanisms in treating HF. It can be further inferred that herbs that tonify *qi* and activate blood may regulate different essential metabolites.

Introduction

Metabolomics, following genomics, transcriptomics, and proteomics, has recently become an important component of systems biology.[1] Metabolomics considers the human body as a complete system, and physiologic and pathologic reactions of the body to both internal and external factors are revealed by changes in metabolism. This perspective coincides with the holistic view and philosophy of traditional Chinese medicine (TCM).

* Corresponding author.
E-mail address: wangwei@bucm.edu.cn (W. Wang).
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Heart failure (HF) is the end stage of various heart diseases. It is one of the most lethal cardiovascular diseases threatening people's health.[2] As such, the medical profession is urgently challenged to address symptoms of this disease and improves the quality of life of HF patients. In China, traditional Chinese medicine (TCM) is often used to treat HF as an adjunct to conventional therapies. For example, a randomized controlled trial found the TCM remedy Astragalus and Lepidium Capsule to Strengthen the Heart (*Qili Qiangxin Jiaonang*) to be efficacious in treating heart failure.[3] However, further research on Chinese herbs that treat HF can help elucidate their mechanism of action, targets, and pathways. Metabolomics may be the key to evaluating the efficacy of Chinese prescriptions through tracking the pathologic metabolites and their changes during treatment, and might serve as a new angle in researching the mechanism of Chinese herbs. A major cause of heart failure is coronary heart disease. Previously, our group conducted a cross-sectional survey of 630 cases of HF which was caused by coronary heart disease.[4] TCM syndrome pattern identification varied from a single pattern to a combination of six patterns, among which the combination of two or three patterns was most frequent, whereas a single pattern was rare. Among patients with a single pattern, *qi* deficiency occurred the most; among patients with two patterns, *qi* deficiency and blood stasis were seen most; among those with three patterns, a pattern of *qi* deficiency, blood stasis, and water retention occurred most frequently.

This current study was conducted using NMR metabolomics to explore the mechanisms of Chinese herbal medicine in treating HF. Changes in metabolites were analyzed to provide further information and reference.

Materials and methods

Participants

A total of 43 inpatients with heart failure from 12 hospitals in China were included in the study. The 12 hospitals were: TCM Hospital of Beijing Huairou (Beijing), Hepingli Hospital (Beijing), Dongzhimen Hospital, Beijing University of Chinese Medicine (Beijing), Xuanwu TCM Hospital (Beijing), Changping Traditional Chinese Medicine Hospital (Beijing), Changping Hospital of Integrated Chinese and Western Medicine (Beijing), Dongfang Hospital, Beijing University of Chinese Medicine (Beijing), Guang'anmen Hospital, China Academy of Chinese Medical Sciences (Beijing), Zhengzhou TCM Hospital (Zhengzhou, Henan), Affiliated Hospital of Changchun University of Chinese Medicine (Changchun, Jilin), Hubei Provincial Hospital of TCM (Wuhan, Hubei), Wuhan Hospital of Traditional Chinese Medicine (Wuhan, Hubei).

In addition, 25 healthy participants in the age-matched control group were enrolled from Dongzhimen Hospital, Beijing University of Chinese Medicine (Beijing).

Diagnostic criteria and TCM pattern identification

Diagnostic criteria were based on *Guidelines for Diagnosis and Treatment of Chronic Heart Failure in China* (2007).[5] TCM pattern diagnosis of HF was based on *Guiding Principles of Clinical Research on New Drugs in Treatment of Heart Failure* (*Trial*), 2002 edition.[6] HF was classified according to the Criteria for Diagnosis and Treatment of Heart Disease first published by the New York Heart Association Functional Classification (NYHA).[7]

Inclusion and exclusion criteria

Patients were included in the study if they were diagnosed with NYHA functional classification II or III (dyspnea, fatigue, edema); were male or female between 40 and 80 years of age. In terms of TCM syndrome pattern, patients had to have been diagnosed with *qi* deficiency, blood stasis, and/or water retention for inclusion.

Patients were excluded if they had any of the following: acute valvular heart disease, cardiomyopathy, pericardial disease, congenital heart disease, acute myocardial infarction within 4 weeks, acute myocarditis or serious arrhythmia with variation in hemodynamics; pulmonary arterial hypertension from cor pulmonale, pulmonary embolism, or stroke within a half year; hepatic insufficiency (liver function 2 times normal), renal insufficiency; hemopoietic diseases, malignancy, diabetes mellitus with serious complications, thyroid disorders; infection, fever, abnormal white blood cell counts; abnormal chest X-ray; mental disorder; pregnant or lactating women; participated in other trials within 2 months. In terms of TCM syndrome pattern, patients who did not present with *qi* deficiency, blood stasis, and/or water retention were excluded.

Ethical issues

This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Dongfang Hospital, Beijing University of Chinese Medicine (approval no. 201002102). All participants signed an informed consent form at the start of the study.

Experimental design

A total of 43 patients were included in the study and were randomly divided into 2 groups: combined treatment group and conventional medicine group. SAS software version 8.1 (SAS Institute, Cary, NC, USA) was used to achieve randomization. Twenty-three participants were assigned to the combined herbal and conventional treatment, and 20 participants were assigned to conventional only treatment.

TCM herbal treatment consisted of herbs in granule form to boost *qi* and activate the blood. The prescription was formulated through data mining of herbs used for heart failure of *qi* deficiency and blood stasis syndrome pattern, and its efficacy had been demonstrated in a previous study.[8] Granules were dissolved in hot water and administered twice a day, once in the morning and evening, with 28 days as a treatment course. Herbs in the formula were astragalus root (Astragalus membranaceus (Fisch.) Bunge.), 60 g; codonopsis root (Codonopsis pilosula (Franch.) Nannf.), 15 g; salvia root (Salviae miltiorrhizae Bunge.), 15