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Plasma metabolomics combined with personalized diagnosis guided by Chinese medicine reveals subtypes of chronic heart failure

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Abstract— An inadequate supply of blood by the heart to fulfil the metabolic needs of the body is a hallmark of chronic heart failure (CHF). The combination of Western and traditional Chinese medicine has been shown to be an effective treatment for congestive heart failure. A promising platform for providing biomarkers for disease subtypes has emerged in the field of metabolomics in recent years.
The purpose of this study was to establish diagnostic biomarkers for two subtypes of congestive heart failure syndrome by combining nuclear magnetic resonance plasma metabolomics with traditional Chinese medicine diagnosis and examining 38 patients.
To analyse the contributing NMR signals, we used Y-scrambling statistical validation, which yielded high reliability. Then, we ran orthogonal partial least square discriminant analysis on the processed spectra.

Patients with yin deficit and yang deficiency were distinguished by their plasma metabolic patterns, according to the results. Lactate, glycoprotein, and lipoprotein levels were higher in the yin-deficiency group, whereas glucose, valine, and proline levels were lower. Lactate, glycoprotein, and pyruvic acid levels were greater in the yang-deficiency group, although glucose and lipoprotein levels were lower.Two TCM symptoms that may serve as biomarkers for congestive heart failure are abnormalities in energy utilisation and disturbances in fatty acid and amino acid metabolism, among other metabolic pathways and metabolites.
This research concludes that metabolic markers for subgroups of CHF syndrome may be revealed by integrating metabolomics with traditional Chinese medical diagnosis. Potentially relevant plasma

Introduction

The progressive clinical illness known as chronic heart failure (CHF) occurs when the heart is unable to pump blood effectively enough to fulfil the body's metabolic needs. It stands as the last common pathway among the many causes of cardiac disease.1 Patients with congestive heart

failure still have a high death rate, even if the survival rate following the beginning of CHF has significantly improved due to the increased use of pharmaceutical therapies. Better strategies for the prevention and treatment of CHF are needed, since the incidence and prevalence of the condition are predicted to rise even more with the ageing population.
Personalised medicine has replaced normal protocol-based illness management as the primary emphasis of Western life sciences, thanks to developments in bioinformatics and healthcare. For thousands of years, traditional Chinese medicine (TCM) has been successfully restoring the human system's self-regulatory abilities via its individualised health approach and methodical diagnostic methods. Echocardiographic measurements, the 6-minute walking distance test, and patients' quality of life are all improved when CHF patients receive treatment that combines traditional Chinese medicine (TCM) with Western medicine. This treatment improves heart function and decreases associated clinical symptoms, such as expiratory dyspnea and chronic fatigue.2 'Syndrome type' refers to systemic dysfunctions, which are also given more weight by TCM doctors.3 It is more than just a collection of symptoms; it's a functional state brought about by responses to or interactions with pathogenic causes and changes in the environment.4 Traditional Chinese Medicine (TCM) "syndrome type" boils down to a human system imbalance that causes changes in the concentration and relative proportions of metabolomics biomarkers as well as disruptions in biological metabolism networks.
An integral part of systematical biology, metabolomics allows for dynamic in vivo and in vitro investigations of healthy tissues and organs utilising non-invasive methods in settings that are very close to their natural habitat.5 Thus, it is possible to get a better understanding of the biochemical alterations linked to illness development via metabolomics detection and analysis of biological materials. Early illness detection and the development of predictive diagnostic systems may be possible with the discovery of metabolic biomarkers linked to certain diseases. The most frequent cardiovascular illness seen in clinical practice, heart failure, reportedly benefits greatly from metab-olomics.6 In recent years, metabolomics has also shown great promise in investigations of TCM. The promise of metabolomics in assessing disease state and TCM-guided personalised treatment has been highlighted by multiple studies7,8 that combined metabolomics methods with TCM syndrome types; these studies showed fingerprints of metabolic changes that characterise diseases diagnosed by Western medicine.

Nuclear magnetic resonance (NMR) spectroscopy, which offers the benefits of high resolution and sensitivity, has been extensively used in metabolomics research and is one of the most popular platforms for metabolomics analysis. The metabolomics pathways and processes underlying CHF may be better understood with the use of NMR while investigating TCM symptoms and treatments.
This study used nuclear magnetic resonance (NMR) spectroscopy to investigate the following in 38 individuals with congestive heart failure (CHF):

(1) potential metabolic biomarkers contributing to discriminate TCM syndrome types (yang-deficiency *vs.* non-yang-deficiency, and yin-deficiency *vs.* non- yin-deficiency); and
(2) similarities and differences in TCM syndrome-related biomarker patterns. We hypothesize that combining TCM diagnosis with metabolomics could provide quantitative biological evidence for TCM diagnosis by identifying CHF subtypes with related plasma meta- bolic patterns.

Materials and methods

Participants and study design

The study was designed as an explorative study without intervention. Patients with a history of coronary heart disease that met the CHF diagnostic criteria in accordance with the Guidelines for the Diagnosis and Management of Chronic Heart Failure established by the Chinese Society of Cardiology of the Chinese Medical Association in 2007 were enrolled. Eligibility criteria were age $\geq$45years and left ventricular ejection fraction $<$50%. All patients were in New York Heart Association (NYHA) classes IIeIV. All patients underwent our standardized recruitment and management. They were diagnosed by two experienced doctors independently to reduce subjective factors. A pre- study screening involved a physical exam that included echocardiography and clinical laboratory tests and was performed immediately. Patients with end-stage renal or liver disease, ongoing infection and long-term immuno- suppressive therapy were excluded.

Thirty-eight patients attending the Heart Diseases

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Clinic at Beijing University of Chinese Medicine Affiliated Hospital from January 2013 to September 2014 were finally enrolled in the study. Samples of venous blood were collected, and the detailed clinical data are shown in Table 1.

The study was approved by the Ethical Committee at the Affiliated Hospital of Beijing University of Chinese Medi- cine, and written informed consent was acquired from all participants recruited.

We used TCM to, investigate general syndromes and classified them into two study groups: (1) yin-deficiency *vs.* non-yin-deficiency (Group 1); and (2) yang-deficiency VS non-yang-deficiency (Group 2). According to *Clinical Terminology of Traditional Chinese Medical Diagnosis and Treatment*d*Syndromes*,[9] yin-deficiency is described as low fever, night sweats, afternoon zygomaticus red, dysphoria with feverish sensation of the chest palms and soles, dry mouth and throat, red tongue with little coating and thready rapid pulse. And yang-deficiency is a cluster of symptoms including an aversion to cold, dispirited feelings and lack of motivation, diarrhea before dawn, shortness of breath, frequent urination, edema, and lia- bility to catch cold. Using these criteria, 15 patients were assessed as being in the yin-deficiency group and 7 pa- tients as being in the yang-deficiency group, others of 38 patients were diagnosed as being in combined syndromes of CHF.

Table 1 Demographic details of participants.

Patients (*n* Z 38)	Mean	SD	Range
Age/years	61.4	5.13	45e79
BMI/kg m^{-2}	28.8	2.4	25.6e35.5
Sex M:F	21/17		e
Median NYHA class	3		e
Mean ejection fraction	54.3	8.2	41e67
Etiology ischemic: non-ischemic	22/16		e
Hypertensive: non-hypertensive	20/18		e
Hyperlipidemia: non-hyperlipidemia	14/24		e
DM: non DM	15/23		e
Smoker: non-smoker	17/21		e
Na+	142.6	4.3	127e147
K+	3.9	0.6	0.9e4.8
Urea	7.1	2.1	3e14
Creatinine	101	32	43e229
Hemoglobin	128.7	20.1	79e175
Beta-blokers Y:N	20/18		e
ACE inhibitors Y:N	14/24		e
Diuretics Y:N	19/19		e

Sample collection and preparation

Clinical parameters included gender, age, ejection frac- tion, creatinine, electrolyte, urea, B-type natriuretic pep- tide, platelet count, hemoglobin, fasting blood glucose, triglyceride levels and total cholesterol. Complications including diabetes, hypertension or dyslipidemia, and drug- taking information of patients were noted at inclusion.

Venous blood of 38 CHF patients at the Heart Failure Clinic were also collected in 5 mL Vacutainer tubes with chelating agent ethylene diamine tetraacetic acid (EDTA)
and centrifuged at 3000 rpm for 10 min. The blood sample was then separated into equal aliquotsand stored at —80◦C until analysis.[10]

For NMR analysis, plasma samples were thawed at room temperature. After being centrifuged at 13 000 rpm for 10 min, 200 mL samples of supernatant were removed. D_2O (400 mL) was added and the mixture was centrifuged again. Following centrifugation, 550 mL of supernatant was trans- ferred to a 5-mm diameter specific NMR tube for NMR analysis. The reaction was performed using a Varian VNMRS 600 MHz NMR spectrometer (Varian Medical Systems, Inc.,
Palo Alto, CA, USA) at 25◦C.

^{1}H-NMR spectroscopy

The spectra were acquired by Carr—Purcell—Meiboom—Gill (CPMG) sequence D-[—90◦-(t-180◦-t)n-ACQ] and Longitudi- nal Eddy-Delay (LED) sequence. Both small molecular me-
tabolites and lipid components in the plasma were observed respectively. The free induction decays were transferred into 64 K data points with a spectral width of 8000 Hz and
64 scans, then zero-filled to double size and multiplied before Fourier transformation, which was applied with an exponential window function to produce a 0.5 Hz broad- ening line. We identified plasma metabolites by comparison with chemical shifts, which is detailed in a previous report.[11]

Spectral and statistical analysis

Spectra were manually phased, baseline corrected and normalized. Each spectrum was referenced using internal lactate CH_3 resonance at d1.33 by Mest-ReNova7.1.0 soft- ware (Mestrelab Research, A Corun˜a, Spain). Signals from d0.5 to d9.0 for each sample were automatically binned with a 0.005 ppm width. Water and EDTA metal complex regions were excluded.[12]

Prior to multivariate data analysis, statistical analyzes were performed on the data using SIMCA-

P+12 software (Umetrics, Umea, Sweden) as variables and then mean- centered and pareto-scaled.

To analyze the NMR data holistically and discriminate CHF patients with different TCM syndrome types and con- trols, we applied both principal component analysis and orthogonal partial least-squares discriminant analysis (OPLS-DA).[13,14]

Score and loading plots were calculated to demonstrate discriminatory metabolites for each group. Each point in a score plot pointed to the projection of a NMR spectrum (patient sample) on the predictive (horizontal axis) and orthogonal components of the model (vertical axis). On the loading plot, positive signals represented those plasma metabolites revealed increased concentrations in CHF pa- tients diagnosed with yin-deficiency or yang-deficiency syndrome. Accordingly, a negative signal corresponded to those down-regulated plasma metabolites.[15]

The key metabolites resulting in discrimination were also analyzed by peak integration. And independent samples *t*-test were used to identify main differences in selected signals.

To obtain a more objective statistical estimation, we performed 'Y-scrambling' validation and calculated R^2 (correlation coefficients) and Q^2 (prediction properties) values to evaluate our OPLS-DA models.[16]

Results

Clinical characteristics of participants

Detailed clinical data characteristics and plasma samples acquired from all CHF patients with different TCM syndrome types were collected. The groups showed no differences in any demographic characteristic, such as gender, age or body mass index.

Metabolomics analysis of plasma samples of CHF with TCM syndromes

As metabolomics has the advantage of being able to identify metabolomics biomarker profiles and reveal relationships among TCM syndrome subtypes, metabolic profiling coupled with multivariate analysis was applied in this study.Based on metabolic profiling, CHF patients with yin-deficiency or yang-deficiency and controls were able to be easily distinguished in principal component analysis score plots. The first two principal components were selected, which described 65.7% of the total variance of the plasma metabolome.

OPLS-DA is a newly developed data analysis method combining orthogonal signal correction and partial least squares, and has been widely used in clinical studies.[10,17] Here, we also performed an OPLS-DA pattern recognition model with one predictive component and four orthogonal components to further identify plasma metabolites that differed in concentrations in CHF patients with different TCM syndrome types. OPLS-DA score plots revealed that yin-deficiency patients were statistically distinguishable from controls (R^2Y = 0.608 Q^2 = 0.327). The former index shows the explanative ability of the syndrome classifica- tion, and the latter is the result of seven-fold cross-vali- dation, and suggests that the OPLS-DA models were robust.[18] The patterns of Group 1 and 2 are clearly distinct from that of the control group along the t[1]-axis direction of the first principle component, without any crossover or overlap (Figs. 1 and 2). This separating trend clearly indicates that metabolic profiling varied according to different TCM syndromes.

Further analysis of loading plots illustrated correspond- ing changes of metabolites of high variable importance, which accounted for metabolomics fingerprint changes and discrimination in score plots. Nine plasma metabolites of yin-deficiency patients and control groups could be determined in the 600 MHz one-dimensional CPMG and LED[1] H- NMR spectra, ranked by the largest variable importance,[19] to be significantly altered metabolites of CHF patients

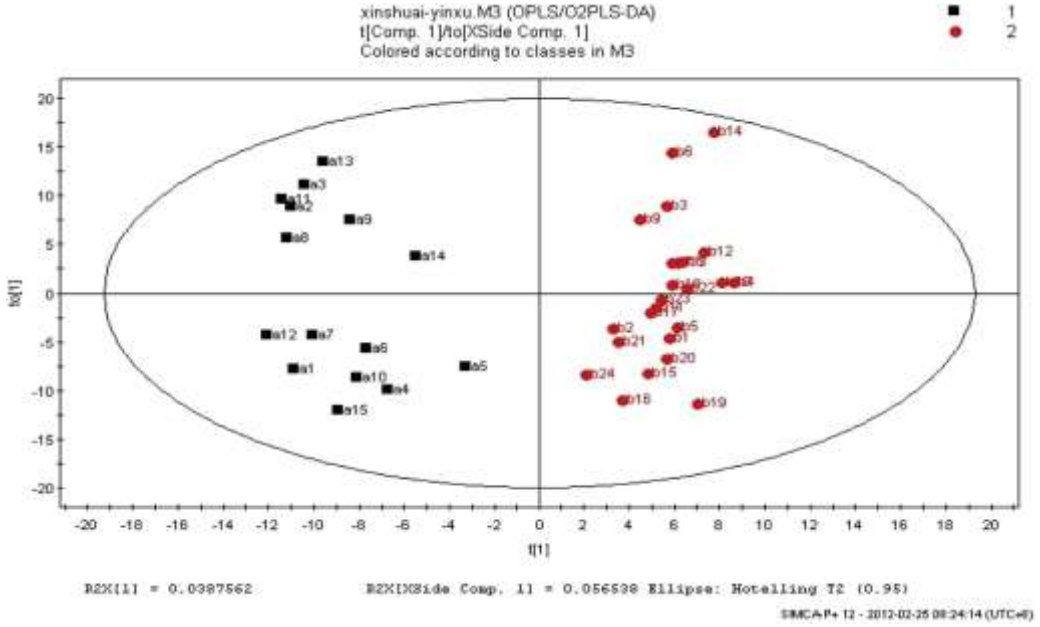

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Fig. 1 OPLS-DA score plots of Group 1. Black box: OPLS-DA score plots displaying discrimination between CHF yang-deficiency patients. Red circle: OPLS-DA score plots displaying discrimination between CHF yang-deficiency controls.

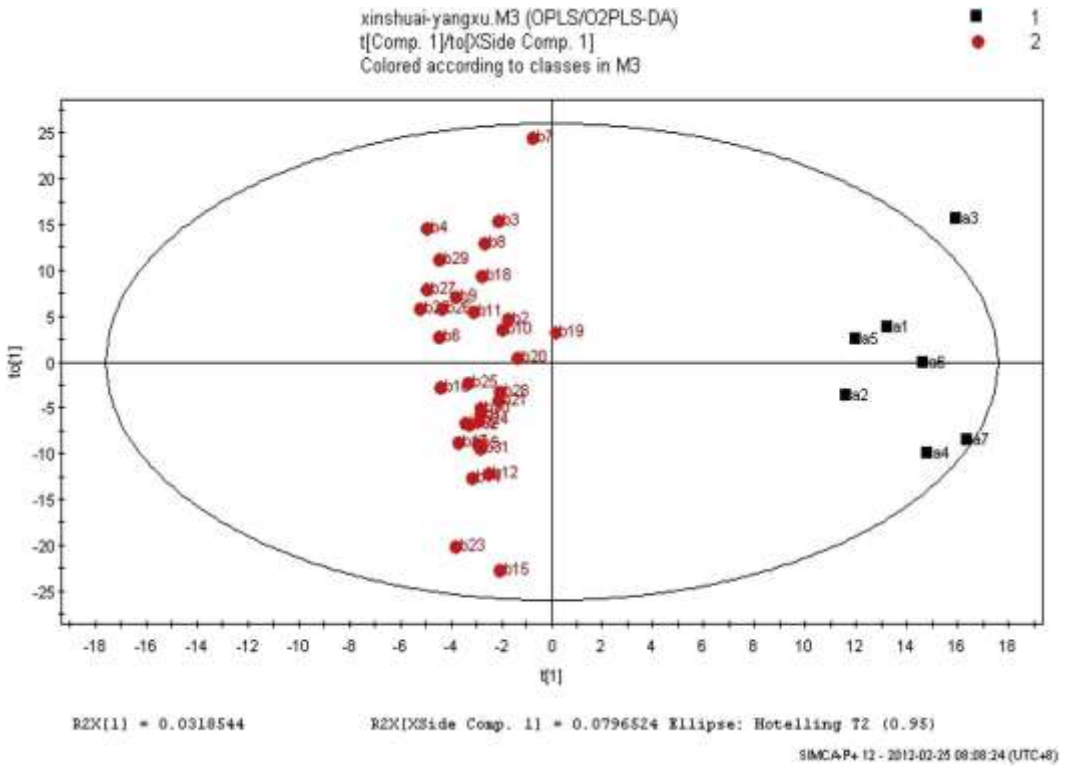

Fig. 2 OPLS-DA score plots of Group 2. Black box: OPLS-DA score plots displaying discrimination between CHF yang-deficiency patients. Red circle: OPLS-DA score plots displaying discrimination between CHF yang-deficiency controls.

with yin-deficiency syndrome (i.e. potential biomarkers) (Figs. 3, 4 and Table 2A). CHF patients with yang-deficiency syndrome were examined as above. Nine metabolites were positively identified as potential biomarkers from variable importance values (Figs. 5, 6 and Table 2B).Statistical validation

We performed 'Y-scrambling' statistical validation to cor- rect chance correlation and evaluate the OPLS-DA model. The Y-variable of case and control group were randomly

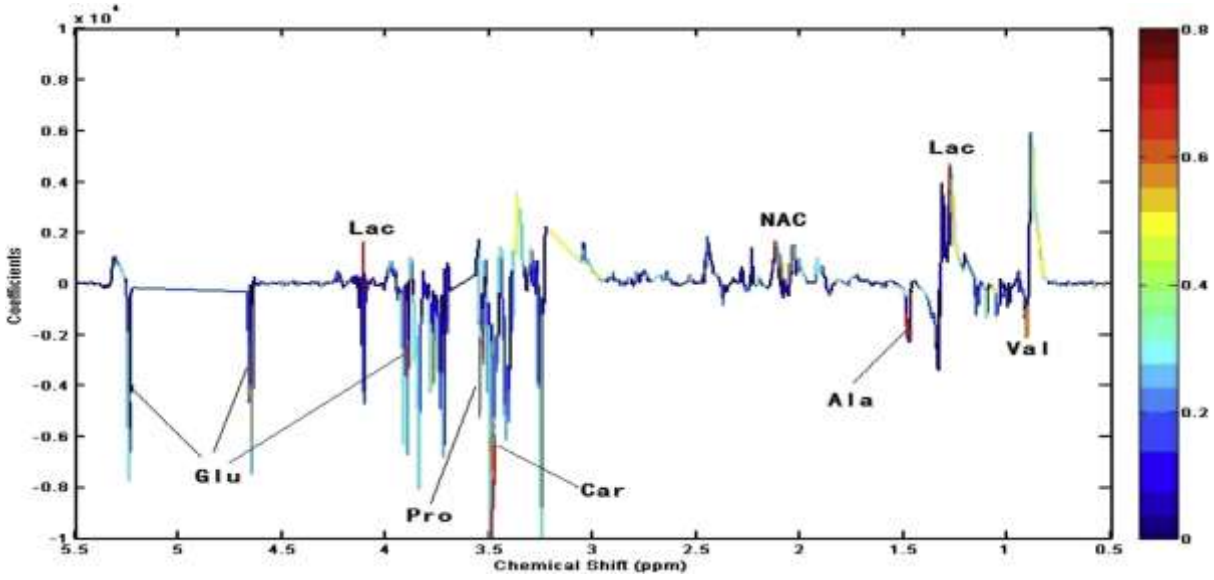

Fig. 3 OPLS-DA loadings plots of key metabolites by CPMG sequence of Group 1. OPLS-DA loadings plots demonstrating discrimination of key metabolite levels between CHF yin-deficiency patients and controls.

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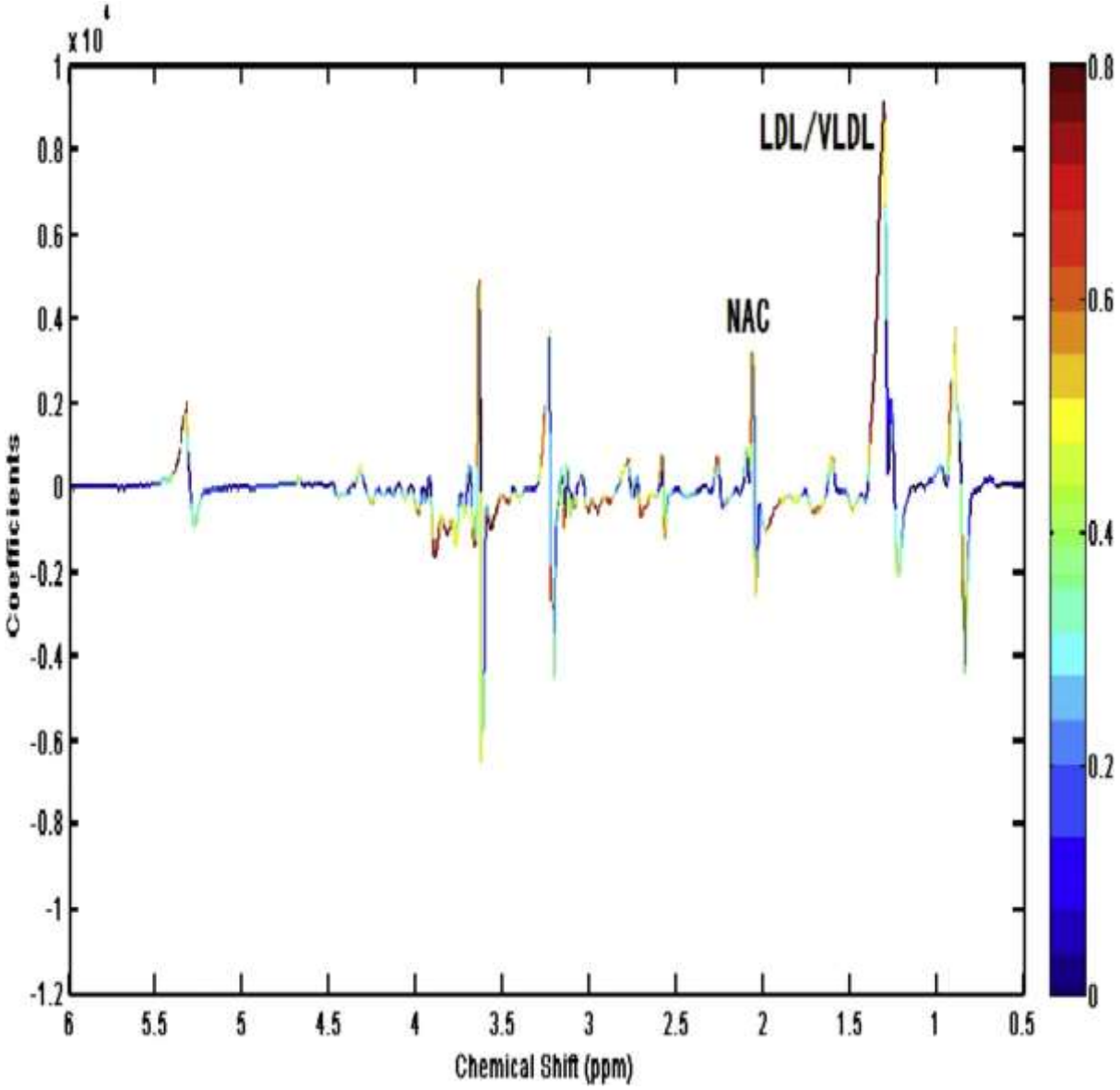

Fig. 4 OPLS-DA loadings plots of key metabolites by LED sequence of Group 1. OPLS-DA loadings plots demonstrating discrimi- nation of key metabolite levels between CHF yin-deficiency patients and controls.

permutated first and the statistical model was rebuilt. In addition, we recorded and analyzed trends of the predictive power and goodness of fit at each step. Two hundred rounds of reshuffling showed that the separation model was reliable, and that its high predictability was not affected by random or over-fitting of the data, as both permutated R^2 and Q^2 values were markedly lower than the corresponding original values (Fig. 7A, B). Even though this study may not include all possible confounding factors in the patients, our validation through randomization of the Y-variable suggests that these variations should not be key attributors for discrimination between case and control groups, or affect the predictability of our model.

Discussion

CHF is clinically associated with high mortality and morbidity, decreased quality of life and substantial burden on health care systems. Despite advances in drug treatment strategies for CHF, the number of deaths resulting from this condition continues to rise.[20] TCM pays particular attention to the integrity and holism of the human body and its inter- relationship

with nature. TCM also adheres to basic princi- ple of treatment based on differentiation of symptoms and signs, treats the same disease by different methods and different diseases by the same method, and advocates individualized treatment, which vividly reflects the essence

Table 2A Key metabolites differentiating CHF yin-deficiency patients and controls.

No	Metabolite	(Chemical shift)	YIP		NYIP		*P*-value	VIP
1	Valine	1.04	0.2526	0.0628	0.3031	0.0507	0.007	1.76
2	VLDL/LDL	1.26, 1.3, 1.34	1.6539	0.0885	1.5791	0.0996	0.010	2.59
3	Lactate	1.33, 4.12	1.4396	0.4708	1.1235	0.2363	0.017	3.99
4	Alanine	1.48	0.2748	0.0873	0.4077	0.1251	0.000	2.11
5	Proline	3.33	0.0353	0.0283	0.0511	0.0226	0.029	3.93
6	Glucose	3.47; 3.72, 4.64, 5.23	4.1008	0.4777	4.7331	0.6542	0.007	3.68
7	Glycoprotein (NeAc)	2.02	0.6093	0.0223	0.4289	0.0696	0.000	2.54
8	Carnitine	2.44	0.0725	0.0138	0.0904	0.0351	0.001	2.39

Abbreviations: YIP, yin-deficiency patients; NYIP, non-yin deficiency patients; LDL, low-density lipoprotein; VLDL, very low-density li- poprotein; HDL, high-density lipoprotein; Values expressed as the mean(SD) (range); P values were calculated from the Independent- samples T Test; Variable importance in the projection (VIP) was acquired from the OPLS-DA model.

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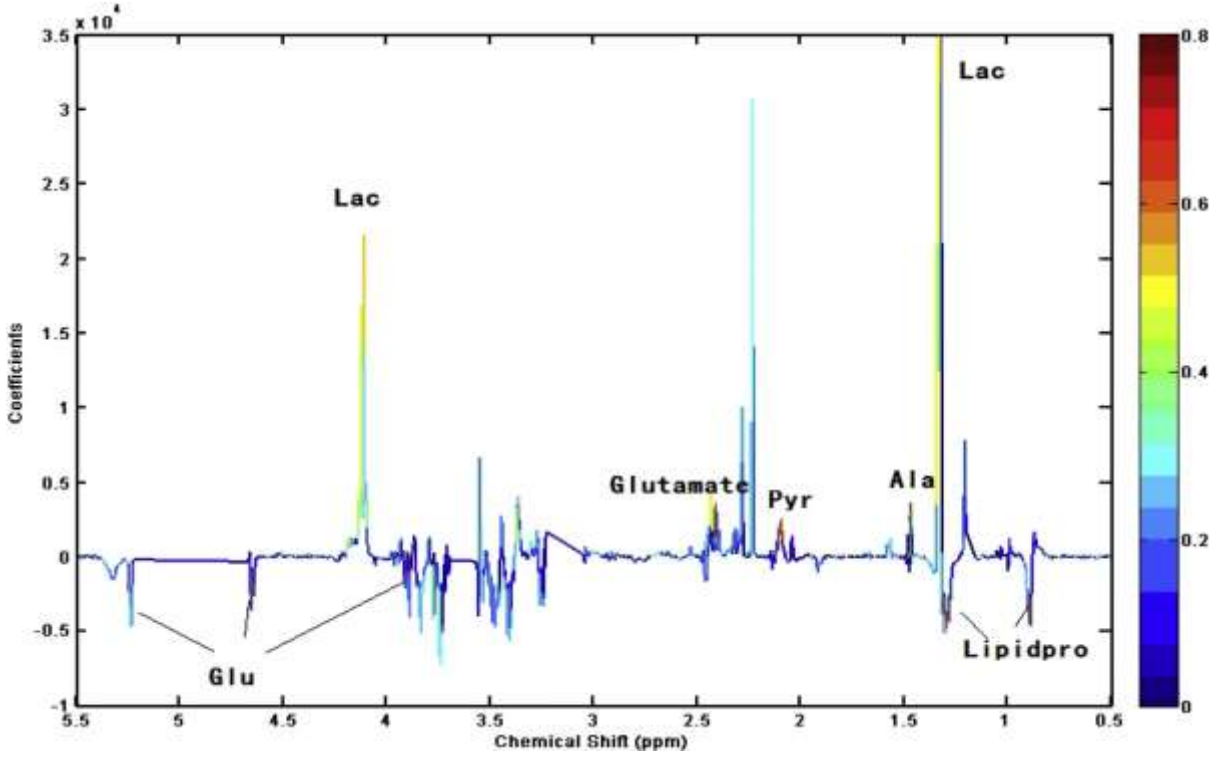

Fig. 5 OPLS-DA loadings plots of key metabolites by CPMG sequence of Group 2. OPLS-DA loadings plots demonstrating discrimination of key metabolite levels between CHF yin-deficiency patients and controls.

TCM treatment.[21] Treatment based on syndrome differ- entiation is at the core of TCM therapy for CHF.

In terms of the perspective of TCM, CHF may occur in all differentiation types, including yang deficiency, blood sta- sis and yin-deficiency, to name a few. Some Chinese herbs have been demonstrated to be safe and effective in the management of CHF in both animal models and in humans.[22,23] Modern biological research has now begun integrating various research technologies and methods to tackle difficult biological problems at bio-molecular levels, which is exemplified by studies in the new scientific field of metabolomics. It is important that potential correlations

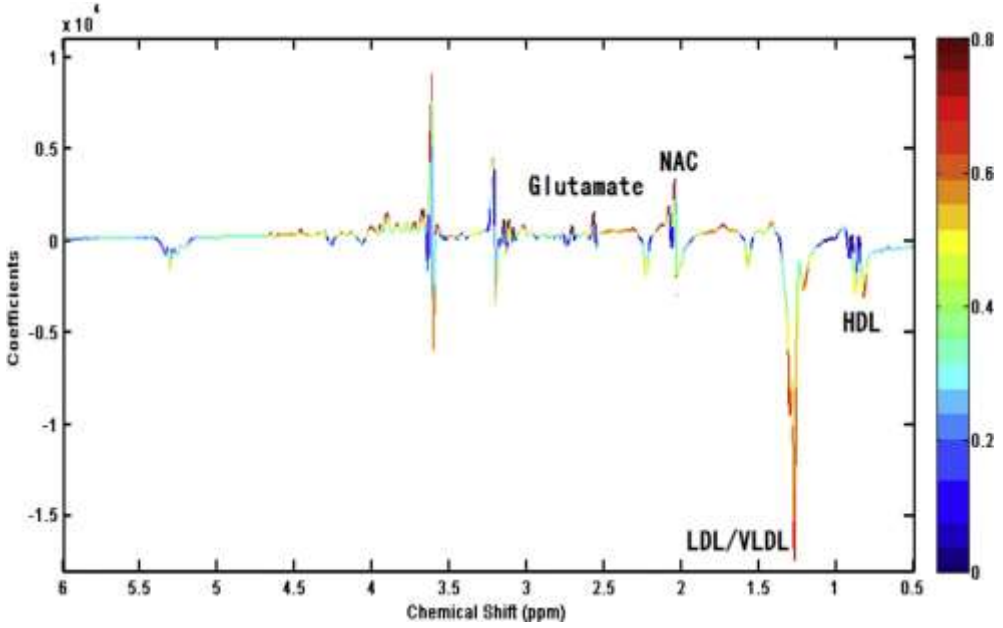

Fig. 6 OPLS-DA loadings plots of key metabolites by LED sequence of Group 2. OPLS-DA loadings plots demonstrating discrimination of key metabolite levels between CHF yin-deficiency patients and controls.

Table 2B Key metabolites differentiating CHF yang-deficiency patients and controls.

No	Metabolite	(Chemical shift)	YADP		NYADP		*P*-Value	VIP
1	HDL	0.82	0.1447	0.0439	0.1979	0.0468	0.0180	2.51
2	Pyruvic acid	0.94	0.0967	0.0181	0.0667	0.0106	0.000	1.45
3	VLDL/LDL	1.26, 1.3, 1.34	1.5539	0.0885	1.8791	0.0996	0.010	2.50
4	Lactate	1.33, 4.12	1.4396	0.4708	1.1235	0.2363	0.017	3.70
5	Alanine	1.48	0.4748	0.0873	0.2077	0.1251	0.000	2.03
6	Glutamate	2.15, 2.52	0.0829	0.0169	0.0586	0.0189	0.000	1.95
7	Glucose	3.47; 3.72, 4.64, 5.23	4.1008	0.4777	4.5371	0.6542	0.007	3.01
8	Glycoprotein (NeAc)	2.02	0.6093	0.0223	0.4289	0.0696	0.000	2.38

Abbreviations: YAP, yang-deficiency patients; NYAP, non-yang deficiency patients; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein. Values are expressed as mean (SD) (range). *P*-values were calculated from independent samples *t*-tests. Variable importance in the projection (VIP) was acquired from the OPLS-DA model.

ln order to find new ways to treat CHF by studying the correlation between TCM symptom type and metabolites.

The purpose of this exploratory investigation was to identify metabolic markers of traditional Chinese medicine (TCM) syndromes in congestive heart failure (CHF) and to develop novel diagnostic techniques in patients with yin-deficiency and yang-deficiency condition. Our method, which included plasma metabolomics in addition to TCM syndrome type identification, demonstrated efficacy across all experimental groups.

We identified distinguishable metabolites that could differentiate CHF patients with each TCM syndrome from controls in this study. These metabolites include energy metabolites (glucose, lactate and glycoprotein), lipid/protein complexes (high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein) and amino acids (alanine, glutamate, valine, glycine, proline and carnitine). These findings provide support for the hypothesis that this metabolomics approach may contribute to our knowledge of TCM symptoms associated with CHF.

This research has some limitations, as do many novel diagnostic techniques. To begin, metabolic profiles might be impacted by various confounding variables. Additionally, this strategy has to be validated by research with bigger cohorts. Secondly, it is challenging to ascribe a

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metabolic fingerprint to certain metabolic activities since plasma samples reflect metabolic processes in several organs.24 Nevertheless, CHF patients exhibiting certain TCM symptoms, which may serve as indicators of illness, have changed metabolite levels to a certain extent. This matter needs more mechanical research.
Levels of glucose, valine, proline, alanine, and carnitine were lower in yin-deficiency patients compared to non-deficiency patients, while levels of lactate, glycoprotein, and LDL/VLDL were higher in yin-deficiency patients.
Patients with congestive heart failure (CHF) who also have yin-deficiency often have abnormalities in energy metabolism, as shown by elevated lactate and hypoglycemia.18 Glycoproteins have an impact on cellular immunity and metabolic energy supply in humans, and they are intricately linked to the pathology and physiology of cell proliferation.25 The most notable difference between the yin-deficiency patients and the control groups was the observation of elevated levels of LDL and VLDL in the CHF patients with yin-deficiency. The significance of apolipoproteins in lipid metabolism suggests that this metabolomics profile may be linked to lipolysis, a pathway for energy utilisation that functions as a backup.
Patients with coronary atherosclerotic disease who also have yin-deficiency syndrome may have elevated proline levels, according to certain reports.26 Alanine and valine are two examples of the well-known non-essential and essential amino acids that are found at low plasma levels in individuals with CHF who have yin-deficiency syndrome. This condition causes a progressive disruption of the body's internal homeostasis. This finding is in agreement with the metabolomics study conducted by Yan et al. in rats with qi-deficiency and yin-deficiency syndromes that demonstrated an association between energy metabolism and oxidative stress response, as well as an increase in inositol and a decrease in valine, glycine, and serine.27 Furthermore, there was a significant decrease in carnitine, a crucial molecule in fat metabolism and energy production, in these individuals. Research has shown that L-carnitine may enhance the absorption of free fatty acids, allowing glucose to be used as an oxidative fuel in some scenarios.28, 29 Inadequate carnitine levels disrupt mitochondrial oxidation, which in turn causes metabolic imbalances and cardiac problems. These metabolic processes include carbs, proteins, and lipids; in patients with congestive heart failure and yin-deficiency syndrome, they are suggestive of a complex metabolic disease.
Secondly, when comparing yang-deficiency patients to non-yang-deficiency patients, the former had lower glucose, LDL/VLDL, and HDL levels and higher lactate, glycoprotein, pyruvic acid, alanine, and glutamate levels. According to traditional Chinese medicine (TCM), yang-deficiency manifests in the latter stages of many illnesses and is characterised by symptoms of persistent weakness, hypofunction, hypometabolism, and degenerative changes.30 Patients with congestive heart failure (CHF) with yang-deficiency had metabolic abnormalities that were highly indicative of carbohydrate and energy metabolism disorders, including decreased glucose metabolism and increased lactate, alanine, and pyruvate. An increase in hepatic gluconeogenesis to produce more pyruvate, a substrate for glucose, may be indicated by a shift in pyruvic acid, suggesting that endogenous glucose synthesis may be augmented.31 The yang-deficiency syndrome is often seen in individuals with stage III and IV CHF, which is in line with our results. There was also an increase in glycoprotein levels.

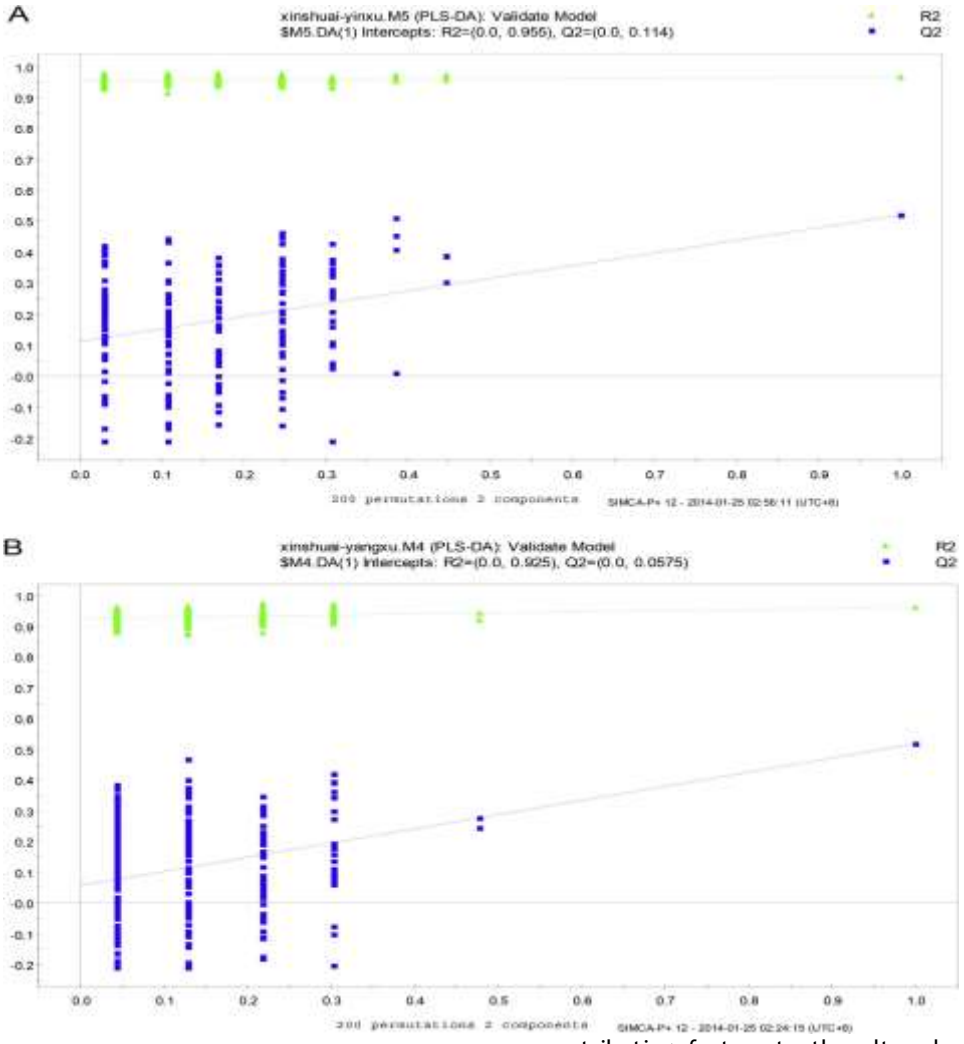

Fig. 7 (A) Statistical validation of the OPLS-DA model of Group 1. A permutation test performed with 200 random permutations in a PLSDA model showing R^2 (green triangles) and Q^2 (blue boxes) values from permuted analysis (bottom left) as significantly lower than corresponding original values (top right). (B) Statistical validation of the OPLS-DA model of Group 2. A permutation test performed with 200 random permutations in a PLSDA model showing R^2 (green triangles) and Q^2 (blue boxes) values from permuted analysis (bottom left) as significantly lower than corresponding original values (top right).

indicate immune defects in patients,[32] while generally lower lipoprotein levels, including LDL/VLDL and HDL, suggest insufficient absorption and utilization of protein during these phases. Higher excretion levels of measured metabolites (glutamate and alanine) in Group 2 partici- pants could indicate further more potential disturbances of renal function, resulting in these patients missing metab- olites necessary for carbohydrate and energy metabolism.[33] A study in China investigated urinary metabolites of yang-deficiency syndrome in patients with chronic kidney disease and reported that key distinguishing metabolites differing between yang-deficiency syndrome patients and the control group included alanine, diethylamine and pro- line.[34] As essential substances in cellular activities, such deficiencies will affect energy supply in all aspects of the human body. These alterations are likely important contributing factors to the altered metabolite profiling of
CHF patients with yang-deficiency syndrome.

This study is an early phase investigation examing TCM syndrome types of CHF based on a small number of study participants. Importantly, this study has demonstrated that two TCM syndromes were able to be distinguished based on their plasma metabolic patterns. While the findings of this study are very promising, further research using larger cohort is required to confirm and validate the reliability of individualized treatment of CHF based on TCM subtypes.

Conclusion

The present investigation sought metabolic subgroups in CHF by combining NMR plasma metabolomics grounded in biology with TCM personalised diagnostics. By analysing metabolic patterns in plasma, researchers were able to distinguish between two kinds of TCM syndrome associated with CHF. The decreased levels of sugars, proteins, lipids, and amino acids in Group 2 as compared to Group 1 suggest that these individuals have more disruptions in energy and carbohydrate metabolism as well as renal function. Plasma metabolites have the potential to

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provide light on metabolomics pathways and prognosis, which might enhance personalised therapies for CHF and aid in the detection of subtypes of the disease. Validation of the TCM subgroups discovered in this research and assessment of intervention responses to prospective metabolic therapies or medications need further investigations.

References

1. Lin et al. (2011) identified molecular markers of advanced heart failure. Published in the Journal of Card Failure in 2011, volume 17, pages 867–874.

Two, Li YL, Ju JQ, Yang CH, and others. Improved quality of life with oral Chinese herbal medicine for patients with chronic heart failure: a meta-analysis and systematic review. Life Science Reviews, 2014, 23, 1177–1192. Thirdly, Jiang WY. Traditional Chinese medicine's therapeutic wisdom: a scientific viewpoint. Current Pharmaceutical Science. 2005;26:558–563.

In the framework of the neuro-endocrine-immune network, Li S, Zhang ZQ, Wu LJ, and colleagues explain ZHENG in traditional Chinese medicine. 2007;1:51–60. IET System Biology.

5. In clinically useful disease biomarkers, metabolites and metabolomics have a role (Mamas M, Dunn WB, Neyses L, et al.). The American Journal of Toxicology; 2011;85:5–17.

6. The authors include Dunn, Broadhurst, Deepak, and others. Metabolomics of serum samples has identified many new biochemical indicators of cardiac failure, such as pseudouridine and 2-oxoglutarate. The journal Metabolomics published an article in 2007 with the DOI 3:413–426.

7. The authors include van Wietmarschen, Yuan, Lu, and others. Chinese medicine-informed systems biology identifies novel subtypes of rheumatoid arthritis. In 2009, the Journal of Clinical Rheumatology published an article spanning pages 330–337.

9. The authors of the study are (Wan JB, Bai X, Cai XJ, etc.). A chemical analysis was conducted on the medicinal Chinese formula Da-Cheng-Qi-Tang utilising a UPLC/Q-TOFMS-based metabolomics methodology, comparing traditional and contemporary decoction procedures. In the Journal of Pharmaceutical Biomedical Sciences, 2013;83:34–42.

Traditional Chinese Medicine State Administration 9. The GB/T16751.2 is the clinical terminology of syndromes in traditional Chinese medicine from 1997.

No. 10: Zheng, Gao, Li, et al. Potentially game-changing diagnostic tool for MDD: plasma metabonomics. In a 2012 article published in the Journal of Proteome Research, Sabatine MS, Liu E, Morrow DA, and colleagues were among the authors. 10. Discovering new indicators of myocardial ischemia using metabolic analysis. Heart. 2005;112:3868e3875.

12. Barton RH, Waterman D, Bonner FW, and colleagues. How adding anticoagulants like EDTA and citrate to human plasma affects data recovery from metabolic profile investigations using nuclear magnetic resonance (NMR) technology. The journal name is "Mol Biosyst" and the reference is 6:215–224.

Thirteen. Brindle, JT, Antti, H, Holmes, E,... Fast and noninvasive evaluation of coronary heart disease severity and existence utilising 1H-NMR-based metabonomics. Natural Medicine, 2002, 8, 1439–1445.

13. Bylesjo¨ M, Cloarec O, Rantalainen M, et al. Combining the strengths of PLS-DA with SIMCA classification: OPLS discriminant analysis. Publication date: 2006, Journal of Chemistry, volume 20, pages 341–351.

Authors: 15. Amathieu, Nahon, Triba, et al. Serum 1H NMR spectroscopy as a metabolomic tool for evaluating cirrhotic patients' chronic liver failure. The citation is from the Journal of Proteome Research, volume 10, pages 3239–3245, 2011.

The authors of the article are 16. Kim K., Aronov P., Zakharkin SO. Analysis of urine metabolomics

with the purpose of detecting kidney cancer and discovering biomarkers. Proteomics in Molecular Cells. 2009;8:558–570.
18. The authors of the study are Kang J, Yoo SS, and Wen H. Novel biliary tract cancer diagnostic method based on nuclear magnetic resonance (NMR) metabolomics. Journal of Hepatology. 2010;52:228–233. 18.Schroe¨n Y, van der Greef J, van Wietmarschen HA, and others. Analysing symptoms, clinical chemistry, and metabolomics profiles in patients treated with Rehmannia six formula (R6): a patient-centered, integrated study. Chapter 19 of the Journal of Ethno-pharmacology (2013).Authors: Eriksson L, Johansson E, Kettaneh-Wold N, and others. Analysing Multi- and Megavariate Data: Theory and Practice. The year 2001, on page 20, was published in Urhea, Sweden.Authors: Desai AS, Claggett B, Pfeffer MA, and others. Mortality among individuals with chronic heart failure throughout the ejection fraction range as a function of whether they were hospitalised for cardiovascular or noncardiovascular causes. Circulation in Heart Failure. November 2014;7:895–900. 21.Duan J, Xu G., Luo X, Lu X, Lu X, Li X. A plasma metabonomics investigation of rheumatoid arthritis subtypes as identified by traditional Chinese medicine utilising gas and liquid chromatography in conjunction with mass spectrometry. Chapter 22 of the book "Molecular Biosyst" (published in 2011) covers pages 2228–2237.Wang X, Li X, Huang J, Zhang J, et al. In a multi-center randomised, double-blind, parallel-group, placebo-controlled trial of Qili Qiangxin capsules in patients with chronic heart failure, the researchers looked at the effectiveness and safety of the supplement. Page 1065–1072 of the 2013 Journal of the American College of Cardiology. 23.Authors: Guo, Yang, Wang, et al. Experimental investigation of the effects of a Chinese herbal decoction on rats with chronic heart failure using meta-analysis. Published in 2014 in the Journal of Chromatography A, volume 1362, pages 89–101.
24. Thom T., Ho K., and Channel WB. Epidemiological aspects of heart failure that are evolving. The authors of the article are Chowdhury, Kehl, Choudhary, and colleagues; the publication is the British Heart Journal, volume 72, issue 2, supplement S3. Application of biomarkers to heart failure patients. Current Cardiology Reports. 2013;15:372.
Youshuai Li, number 26. Analysing the Metabolites and Constitutional Theory of Yang Deficiency and Yin Deficiency in Comparison [dissertation]. Journal of Beijing University of Traditional Chinese Medicine, Beijing, China, 2009: 56–90 [Chinese].
28. Yan B, Hao HP, Justice A, et al. Characteristics of metabonomics, include the identification of the "heart blood stasis blockage pattern" and the "qi

the "yin deficiency pattern" in rats with myocardial ischemia... Scientific Chinese Supplementary Articles in Life Sciences. 2009;52:1081–1090 [Chinese].
Y. Mardens, A. Kumps, and P. Duez. Purine organic acid sources: a comprehensive table including metabolic, dietary, iatrogenic, and artifactual factors. Journal of Clinical Chemistry, 2002, 48: 708–717. 29. Wei H, Pasman W, Rubingh C, et al. Multiple subgroups of pre-diabetes have been identified by the integration of urine metabolomics with personalised diagnostics aided by Chinese medicine. Journal of Molecular Biosystems, 2012, 8, 1482–1491. (p. 30).By Tan Y, Liu X, Lu C,, and colleagues. In rats treated with hydrocortisone-induced kidney disease, metabolic profiling revealed therapeutic indicators of processed Aconitum Carmichaeli Debx. Article cited as "J Ethnopharmacol" in 2014, volume 152, pages 585–593. Authors Connor, Hansen, Corner, et al. Using combined meta- and transcriptomics data to better identify type 2 diabetes biomarkers. Vol. 6, Issue 9, Pages 909–921, in Mol. Biosyst. (2010), by Tedeschi, Pilotti, Parenti, and others. Cachectic versus non-cachectic heart failure patients' serum adipokines zinc a2-glycoprotein and lipolysis: correlation with neuro-hormonal and inflammatory indicators. Li X, Luo X, Lu X, et al. (2012) published in Metabolism, volume 61, pages 37–42. Metabolomics investigation of diabetic reti- nopathy using gas chromatographyemass spectrometry: a comparison of stages and subtypes identified by Western and Chinese medicine. Molecular Biosystems. 2011;7:2228–2237. 34.Citation: Dong F, Huang D, He L, et al. Research on the metabolic analysis of urine in patients with chronic kidney disease (CKD) and renal-yang deficit. Chinese Journal of Traditional Chinese Medicine and Pharmacy, 2008, 12:1110–1113.

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