Qishentaohong Granule as Adjuvant Therapy for Improving Cardiac Function and Quality of Life in Patients with Chronic Heart Failure: a Randomized Controlled Trial

Xing-xing Li  
Beijing University of Chinese Medicine

Zong-Jing Fan  
Dongfang Hospital, Beijing University of Chinese Medicine

Jie Cui  
Dongfang Hospital, Beijing University of Chinese Medicine

Quan Lin  
Xiyuan Hospital, China Academy of Chinese Medical Sciences

Qian Lin  
Dongzhimen Hospital, Beijing University of Chinese Medicine

Rong-Kun Yan  
Beijing University of Chinese Medicine

Yang Wu  
Dongfang Hospital, Beijing University of Chinese Medicine

Yan Li  
15801434320@163.com  
Dongfang Hospital, Beijing University of Chinese Medicine

Research

Keywords: Chronic heart failure, Traditional Chinese medicine, Qishentaohong granule, Cardiac function, Quality of life

DOI: https://doi.org/10.21203/rs.3.rs-45957/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

**Background:** Qishentaohong Granule (QSG) is a traditional Chinese medicine (TCM) prescription for the treatment of chronic heart failure (CHF). The objective is to confirm the improvement of QSG on cardiac function and quality of life (QOL) in patients with CHF.

**Methods:** This is a single-center, prospective, randomized controlled clinical trial. Seventy-six patients (forty-four male and twenty-six female) from 27 to 84 years old with diagnosed CHF New York Heart Association (NYHA) class or in stage C were enrolled and randomly assigned in a 1:1 ratio to receive the QSG (9 g, twice daily) or trimetazidine (TMZ) (10 mg, thrice daily) in addition to their standard medications for the treatment of CHF. The study period was 4 weeks. The primary outcomes (cardiac function and QOL) and secondary outcomes were measured at the baseline and end of the trial.

**Results:** Thirty-five patients completed the study in each group. At the 4-week follow-up, the effective rate in NYHA classification in the QSG group was better than that in the TMZ group (74.29% vs. 54.29%, \(P<0.05\)). Chronic heart failure integrated traditional Chinese and Western medicine survival scale (CHFQLS) scores were improved by 13.82 ± 6.04 vs. 7.49 ± 2.28 in the QSG and TMZ groups respectively (\(P<0.05\)). Subgroup analysis of the CHFQLS results showed that physiological function, role limitation and vitality were significantly higher in the QSG group (15.76 ± 7.85 vs. 7.40 ± 3.36, \(P<0.05\); 16.00 ± 8.35 vs. 10.53 ± 4.64, \(P<0.05\); 15.31 ± 8.09 vs. 7.89 ± 4.60, \(P<0.05\)). Treatment with QSG also demonstrated superior performance in comparison to the TMZ with respect to 6-minute walking test (6MWT), TCM syndrome, shortness of breath, fatigue, gasp, general edema and the N-terminal pro-B-type natriuretic peptide (NT-proBNP) level. No significant adverse reactions (ARs) and adverse cardiac events (ACEs) occurred during treatment in either group.

**Conclusion:** In addition to conventional treatments, QSG as an adjuvant therapy significantly improved cardiac function and QOL in patients with CHF class or in stage C.

**Trial registration:** This trial is registered with ChiCTR, No. ChiCTR-TRC-12002857. Registered March 21, 2019. (retrospectively registered)

Introduction

Chronic heart failure (CHF) has become a disorder of epidemic proportions worldwide over the past 5 decades as mortality from atherosclerotic cardiovascular disease have dropped dramatically and life expectancy has increased [1]. Patients with CHF typically experience impaired quality of life (QOL) [2]. Therefore, it is time for clinicians to develop innovative alternative and complementary treatments that can improve QOL for CHF patients.

Professor Liao Jia-zhen and Professor Lin Qian, illustrious veteran traditional Chinese medicine (TCM) doctors, concluded that the basic pathogenesis of CHF is the interaction of qi deficiency, blood stasis and water retention [3]. With the method of tonifying qi, promoting blood circulation by removing blood stasis...
and inducing diuresis to alleviate edema, they formulated Qishentaohong Granule (QSG, original name: Yiqi Huoxue Lishui prescription). QSG has obtained the national patent of China (No. 201711129837.6) and has shown satisfactory efficacy in clinic for the treatment of CHF.

In this prescription, *Astragalus membranaceus* and *Codonopsis pilosula*, as monarch medicines, can replenish the heart, spleen, lung qi and thoracic qi, which can make the blood flow smoothly. *Salvia miltiorrhize*, *Semen persicae* and *Carthamus tinctorius* can promote blood circulation to remove blood stasis so that the blood flows smoothly, qi is tonified without leaving any stagnation, and the internal organs are nurtured so that they can be used to perform normal gasification functions. *Cortex mori*, *Semen lepidii*, *Polyporus umbellatus* and *Lycopus lucidus* can play a role in inducing diuresis to alleviate edema.

Insufficient myocardial energy production and/or energy metabolism disorders are important pathogenesis in the development of CHF [4]. As the driving force of human life activities, the "energy" in modern medicine is highly analogous to the "qi" in TCM [4]. Previous studies have found that Chinese herbal medicine with qi-invigorating effect can significantly improve the myocardial energy substances ATP and PCr in rats with heart failure [5]. TMZ, which are known to regulate myocardial energy metabolism, are commonly used in the treatment of heart failure to optimize energy metabolism substrates and promote glucose metabolism [6].

In this study, we therefore investigated the effects of QSG on cardiac function and QOL in CHF patients, using TMZ as a positive control drug.

**Materials And Methods**

**Ethics and trial registration**

The research was approved by the Ethics Committee of Dongfang Hospital Affiliated to Beijing University of Chinese Medicine (JDF-IRB-2017030402) and registered at www.chictr.org.cn (Identifier: ChiCTR-TRC-12002857). The implementation of this study adhered to the guidelines of the Declaration of Helsinki and Tokyo for humans.

**Study design**

This single-center, prospective, randomized controlled clinical trial was conducted at Dongfang Hospital Affiliated to Beijing University of Chinese Medicine in China between March 2017 and September 2019. All the subjects were inpatients and gave informed consent before the trial began.

**Subjects**

**Inclusion criteria**
Men and women between the ages of 18–84 years old who have been diagnosed with CHF, classified as NYHA grade II or III and ACC/AHA stage C, and diagnosed with the syndrome of qi deficiency, blood stasis and water retention based on TCM syndrome differentiation were eligible for inclusion in this trial.

**Exclusion Criteria**

Patients who met any of the following criteria were excluded from this trial: (1) acute myocardial infarction, cardiogenic shock, lethal cardiac arrhythmias, cardiac tamponade, pulmonary embolism, acute myocardial infarction, and other severe conditions; (2) serious primary diseases of lung, liver, kidney, endocrine system, or hematological system; (3) pregnancy or lactation; (4) allergic constitution or allergy to multiple drugs; (5) patients with mental illness, mental disorders, dementia or malignant tumor; (6) participants who have taken Chinese medicine (including proprietary Chinese medicines) or participated in other clinical trials in the past 2 weeks; and (7) patients who had incomplete clinical data.

**Elimination and termination criteria**

Patients were removed from the study if they met any of the following criteria: (1) noncompliance with research protocols; (2) dropping out during the trial; (3) failing to take drugs regularly and completing follow-up in a timely manner; (4) serious allergic reactions or adverse reactions; or (5) patient death during follow-up.

**Outcomes**

**Primary Outcomes**

The following observation indexes were collected at baseline and 4 weeks. (1) Cardiac function: NYHA classification

[Efficiency standard [7]: Excellent: heart failure was essentially ameliorated or the NYHA classification increased by at least 2 levels; Valid: NYHA classification increased by 1 level; Invalid: NYHA classification remained the same before and after the treatment; Worsened: NYHA classification decreased by at least 1 level].

2. Left ventricular ejection fraction (LVEF); (2) QOL measured by CHFQLS [8]. The CHFQLS has a total of 39 items, which can be divided into 6 dimensions, including 17 items about physiological function, 7 items about role limitation, 5 items about vitality, 4 items about social function, 3 items about mental health and 2 items about medical support, and the last one is overall health satisfaction, which is not included in the total score. The answer to each question was graded as 0, 1, 2, 3, 4, or 5 points, with higher conversion scores representing better QOL. Conversion score = (highest score possible in this field - original score) / highest score possible in this field.

**Secondary Outcomes**

Endpoints as followed were recorded before and after treatment. (1) 6MWT; (2) TCM syndrome score calculated by symptom score plus sign score; (3) Symptom score: each main symptom scored as 0, 2, 4, or 6 points, or 0, 3, 6, or 9 points; each secondary symptom scored as 0, 1, 2, or 3 points. A higher score
indicates poorer condition; (4) Sign score observed was blood stasis syndrome which scored as 0, 3, 6, or 9 points, with higher scores representing poorer condition; (5) NT-proBNP.

**Safety Outcomes**

ARs and ACEs were recorded during the treatment. The ACEs included acute coronary syndrome, reinterventional therapy, coronary artery bypass grafting, malignant arrhythmia, recurrent angina and severe heart failure (NYHA classification IV), stroke and death.

**Sample Size**

Sample size estimation was based on the result reported in the previous literature [9], and the effective rate of the Chinese medicine treatment group and the control group was 85% and 52.5%, respectively. Specifically, the two-tailed alpha level was 0.05, and the beta level was 0.20. According to the formula below, we calculated that 34 patients were needed for each group with a ratio of 1:1. Assuming a dropout rate of 10%, the sample size was 76.

\[
\begin{align*}
n &= (\mu_a + \mu_b) \times 2P \times \frac{(1-P)}{(P_1 - P_2)^2} \\
P &= \frac{(P_1 + P_2)}{2} \\
\mu_a &= 1.65, \quad \mu_b = 1.28
\end{align*}
\]

**Random implementation**

A random number table [10] was used to randomly allocate seventy-six individuals into the QSG group (n = 38) and the TMZ group (n = 38); then, they were coded A and B, respectively. Seventy-six opaque envelopes were used. A number between 1 and 76 was written on each envelope, and the group allocation was written inside the envelopes. The envelopes were used to randomly assign patients to groups; the envelope was no longer used if the participant was excluded or terminated.

**Intervention**

All patients received conventional Western treatment according to the Chinese guidelines published in 2018 for the diagnosis and treatment of heart failure [11], which includes diuretics, angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), β-receptor blockers, aldosterone-receptor blockers, etc. Moreover, patients in the QSG group were treated with QSG (9 g/pouch, twice per day) dissolved in warm water, and patients in the TMZ group were treated with 10-mg trimetazidine dihydrochloride tablet (Beijing Wansheng Pharmaceutical Co., Ltd. (Beijing, China), 20 mg per tablet, batch number: 31610009) 3 times a day. The treatment period was 4 weeks.
The drugs for the treatment of hypertension, diabetes mellitus, dyslipidemia and other diseases could be used reasonably.

**Preparation of QSG**

QSG prepared and provided by Beijing Kangrentang Pharmaceutical Co., Ltd. (Beijing, China). One dose of QSG consisted of the following: *Astragalus membranaceus* 30 grams (g), *Codonopsis pilosula* 15 g, *Salvia miltiorrhize* 15 g, *Semen persicae* 10 g, *Carthamus tinctorius* 10 g, *Cortex mori* 10 g, *Semen lepidii* 15 g, *Polyporus umbellatus* 15 g and *Lycopus lucidus* 15 g. These ingredients were soaked in distilled water for 30 minutes, boiled in water for 1 hour, extracted with water twice, filtered and concentrated to a concentration of 1 g/ml, and finally, processed into particles through spray drying.

**Statistical analysis**

All data were analyzed using the Statistical Product and Service Solutions (SPSS) 20.0 (Shanghai Cabit Information Technology Co., Ltd.) software package. Continuous data are expressed as the mean ± standard deviation (SD), and categorical data are expressed as percentages or frequencies. For normally distributed variables, comparisons between the treatment group and control group were conducted by independent t-tests, and comparisons within each group were analyzed by paired t-tests; for non-normally distributed variables, nonparametric tests were used. Categorical variables were analyzed using the chi-squared test or Wilcoxon test. \( P < 0.05 \) indicated that the difference was statistically significant, and all tests were two-tailed.

**Results**

From March 2017 to September 2019, 90 CHF patients were considered eligible. Due to multiple reasons, only 76 patients were enrolled in this study and assigned to the QSG group and TMZ group at a 1:1 ratio (QSG group \( n = 38 \); TMZ group \( n = 38 \)). Of the 76 patients who were included, 6 (7.8%) dropped out during the treatment. There were no significant differences in baseline characteristics between the two groups. The reasons for attrition included loss to follow-up, withdrawal, adverse events and other reasons (Fig. 1).

**Baseline characteristics**

The baseline characteristics of the two groups are shown in Table 1. The QSG group and the TMZ group were balanced with respect to the baseline characteristics.
### Table 1
**Baseline characteristics**

| Characteristics                  | QSG (n = 35) | TMZ (n = 35) | P value |
|----------------------------------|--------------|--------------|---------|
| Demographics                     |              |              |         |
| Age (Year, mean ± SD)            | 67.89 ± 10.77| 67.66 ± 11.17| 0.931   |
| Male/Female                      | 24/11        | 20/15        | 0.322   |
| Course of disease [n (%)]        |              |              | 0.603   |
| ≤ 1 year                         | 13 (37.14)   | 9 (25.71)    |         |
| 1 year ~ 5 years                 | 5 (14.29)    | 8 (22.86)    |         |
| ≥ 5 years                        | 17 (48.57)   | 18 (51.43)   |         |
| Basic disease [n (%)]            |              |              | 0.642   |
| CHD1                             | 24 (68.57)   | 27 (77.15)   |         |
| HHD                              | 4 (11.43)    | 2 (5.71)     |         |
| DCM                              | 3 (8.57)     | 1 (2.86)     |         |
| RHD                              | 2 (5.71)     | 3 (8.57)     |         |
| PHD                              | 1 (2.86)     | 2 (5.71)     |         |
| CHD2                             | 1 (2.86)     | 0 (0)        |         |
| Medication [n (%)]               |              |              |         |
| ACEI                             | 17(48.57)    | 19(54.29)    | 0.632   |

**Notes**: CHF, chronic heart failure; CHD1, coronary heart disease; RHD, rheumatic heart disease; DCM, dilated cardiomyopathy; PHD, pulmonary heart disease; HHD, hypertensive heart disease; CHD2, congenital heart disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 6MWT, 6 minutes walking test; ACEI, angiotension converting enzyme inhibitors; ARB, angiotensin-receptor blocker; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. CHFQLS, chronic heart failure integrated traditional Chinese and Western medicine survival scale.
| Characteristics          | QSG (n = 35) | TMZ (n = 35) | P value |
|--------------------------|--------------|--------------|---------|
| ARB                      | 17(48.57)    | 16(45.71)    | 0.811   |
| Beta-blockers            | 25(71.43)    | 28(80.00)    | 0.403   |
| Digoxin                  | 11(31.43)    | 10(28.57)    | 0.794   |
| Diuretic                 | 25(71.43)    | 29(82.86)    | 0.255   |
| Spironolactone           | 15(42.86)    | 12(34.29)    | 0.461   |

Primary outcomes

| NYHA classification [n (%)] |         |         | 0.553   |
|-----------------------------|---------|---------|---------|
| I                           | 0 (0)   | 0 (0)   |         |
| II                          | 8 (22.86) | 6 (17.14) |       |
| III                         | 27 (77.14) | 29 (82.86) |   |
| IV                          | 0 (0)   | 0 (0)   |         |

LVEF (%, mean ± SD)

| QSG              | TMZ              | P value |
|------------------|------------------|---------|
| 35.86 ± 8.18     | 37.31 ± 7.71     | 0.387   |

CHFQLS (Score, mean ± SD)

| Characteristics       | QSG              | TMZ              | P value |
|-----------------------|------------------|------------------|---------|
| Total score           | 58.84 ± 12.26    | 59.97 ± 11.94    | 0.742   |
| Physiology            | 60.34 ± 14.16    | 62.35 ± 14.72    | 0.561   |
| Role limitation       | 61.23 ± 13.19    | 60.00 ± 15.32    | 0.782   |
| Vitality              | 56.57 ± 11.07    | 57.14 ± 14.95    | 0.595   |
| Social function       | 59.86 ± 16.20    | 61.29 ± 12.68    | 0.939   |

Notes: CHF, chronic heart failure; CHD1, coronary heart disease; RHD, rheumatic heart disease; DCM, dilated cardiomyopathy; PHD, pulmonary heart disease; HHD, hypertensive heart disease; CHD2, congenital heart disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 6MWT, 6 minutes walking test; ACEI, angiotension converting enzyme inhibitors; ARB, angiotensin-receptor blocker; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. CHFQLS, chronic heart failure integrated traditional Chinese and Western medicine survival scale.
| Characteristics                        | QSG (n = 35) | TMZ (n = 35) | P value |
|----------------------------------------|--------------|--------------|---------|
| Mental health                          | 54.48 ± 21.11| 56.76 ± 12.67| 0.804   |
| Medical support                        | 48.00 ± 13.46| 48.86 ± 16.05| 0.619   |
| Secondary outcomes                     |              |              |         |
| TCM syndrome scores                    | 20.17 ± 5.18 | 20.23 ± 4.14 | 0.723   |
| (Score, mean ± SD)                     |              |              |         |
| Symptom or sign score                  |              |              |         |
| (Score, mean ± SD)                     |              |              |         |
| Shortness of breath                    | 4.00 ± 1.53  | 4.40 ± 1.44  | 0.269   |
| Fatigue                                | 4.06 ± 1.57  | 4.46 ± 1.46  | 0.243   |
| Gasp                                   | 1.69 ± 0.87  | 1.34 ± 0.76  | 0.132   |
| Palpitation                            | 1.43 ± 1.09  | 1.00 ± 0.77  | 0.116   |
| Chest ctightness or chest pain         | 3.00 ± 1.78  | 2.86 ± 1.71  | 0.717   |
| Blood stasis syndrome                  | 3.43 ± 1.80  | 3.77 ± 1.68  | 0.433   |
| General edema                          | 1.80 ± 0.83  | 1.80 ± 0.83  | 1.000   |
| Abdominal distention                   | 0.77 ± 0.69  | 0.57 ± 0.56  | 0.243   |
| 6MWT (Meter, mean ± SD)                | 160.29 ± 56.65| 180.16 ± 69.08| 0.267   |
| NT-proBNP (ng/L, mean ± SD)            | 4748.09 ± 3323.05| 4657.73 ± 3611.57| 0.720   |

*Notes:* CHF, chronic heart failure; CHD1, coronary heart disease; RHD, rheumatic heart disease; DCM, dilated cardiomyopathy; PHD, pulmonary heart disease; HHD, hypertensive heart disease; CHD2, congenital heart disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 6MWT, 6 minutes walking test; ACEI, angiotension converting enzyme inhibitors; ARB, angiotensin-receptor blocker; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association. CHFQLS, chronic heart failure integrated traditional Chinese and Western medicine survival scale.

**Comparison of primary outcomes in each group**

**NYHA functional classification**

QSG treatment significantly improved the NYHA classification by 74.29% compared to the 54.29% increase observed in the TMZ group ($P = 0.036 < 0.05$; Table 2).
Table 2
Comparison of the NYHA Functional Classification between the two groups [n (%)]

| Group     | Excellent | Valid     | Invalid | Worsened | Effective rate |
|-----------|-----------|-----------|---------|-----------|----------------|
| QSG (n = 35) | 10 (28.57)| 16 (45.72)| 9 (25.71)| 0 (0)     | 74.29%△        |
| TMZ (n = 35) | 4 (11.43)| 15 (42.86)| 16 (45.71)| 0 (0)     | 54.29%         |

Note: Effective rate was defined as proportion of all patients who experienced an excellent or valid outcome; △ P < 0.05, compared with the TMZ group.

LVEF

As shown in Table 3, the baseline LVEF was 35.86 ± 8.18 in the QSG group and 37.31 ± 7.71 in the TMZ group. After 4 weeks of treatment, the LVEF increased to 39.94 ± 9.86 in the QSG group and to 39.82 ± 7.88 in the TMZ group. There was no significant difference in post-treatment level of LVEF and change of LVEF between the two groups (P > 0.05).

Table 3
Comparison of LVEF between the two groups

| Characteristics | QSG | TMZ | P   | P  | P     |
|-----------------|-----|-----|-----|----|-------|
|                 | Baseline | 4 Weeks |  | Baseline | 4 Weeks |  |
| LVEF, %         | 35.86 ± 8.18 | 39.94 ± 9.86* | < 0.001 | 37.31 ± 7.71 | 39.82 ± 7.88* | 0.002 | 0.865 |
| Change, %       | 4.09 ± 4.82 | 2.51 ± 4.59 | 0.145 |

Note: Values are expressed as mean ± SD. Change = 4-week level – baseline level. * P < 0.05, compared with the same group at baseline. △ P < 0.05, compared with the TMZ group at the same time-points;

CHFQLS score

The comparison of the CHFQLS scores is shown in Fig. 2. After 4 weeks of treatment, all patients experienced a remarkable increase in CHFQLS score (P < 0.05 for all). Specifically, there were statistically significant differences in the total score, physiological function, role limitation and vitality scores and their change over the duration of treatment between the two groups after treatment (P < 0.05 for all). However, there was no significant difference in social function, mental health and medical support score and the change after treatment between two groups (P > 0.05).

Comparison of secondary outcomes in each group

TCM syndrome, symptom and sign scores
Over the 4-week treatment period, there was a gradual decrease in the TCM syndrome score in both the QSG (20.17 ± 5.18 to 8.80 ± 4.96) and the TMZ group (20.23 ± 4.14 to 12.66 ± 5.11). Specifically, the improvements in shortness of breath, fatigue, gasp and general edema were greater in the QSG group than in the TMZ group (P < 0.05 for all). Although there were significant differences in the scores of palpitation, chest tightness or chest pain, blood stasis syndrome and abdominal distention in each group after 4 weeks of treatment, the changes in these parameters across the treatment were not significantly different between the groups (P > 0.05 for all), as shown in Fig. 3.

6MWT and NT-proBNP

As measured by the 6MWT at the end of the intervention, the walking distance of participants in the treatment group increased by 157.27 ± 65.60 m, which was higher than the increase of 107.85 ± 68.38 m in the control group (P = 0.01, Fig. 4a). As shown in Fig. 4b, there was improvement in the NT-proBNP levels during the process of this study; the treatment group had markedly lower NT-proBNP levels than the control group after 4 weeks of treatment (P = 0.038). And the change in NT-proBNP levels was significantly different between the two groups (P = 0.394).

Safety evaluation.

No significant ARs or ACEs were reported during the treatment, which proves that QSG is safe for clinical use.

Discussion

Our study demonstrated that in the setting of CHF class II and III in stage C, Chinese prescription QSG enhanced cardiac function and QOL, improved exercise tolerance, TCM syndrome and symptoms or signs, and decreased NT-proBNP levels.

CHF is the end stage of various cardiovascular diseases and the 1-year mortality of severe patients is as high as 10% [12]. TCM has a long history and definite curative effect for treatment of CHF [13]. Chinese herbs, which are the most critical component of TCM, are widely used in China. The interaction of qi deficiency, blood stasis and water retention is regarded as the main pathological change in CHF according to TCM theory [3]. QSG is a Chinese prescription that enriches qi, promotes blood circulation, and removes water retention. A variety of Chinese herbs in QSG have been proven to have anti-heart failure effects [14–17].

As a simple and easy measure, NYHA can reflect the severity of heart failure and is related to objective indicators of exercise [18, 19]. The results illustrated that QSG plus standard Western medicine therapy led to greater improvements in NYHA classification than the TMZ group, which coincided with improved 6MWT and NT-proBNP levels. However, there were no statistical differences in LVEF between the two groups after treatment, which might be related to limited follow-up time and the small sample size. And it also indicated that the improvement of the NYHA classification, clinical symptoms and 6MWT in patients.
with CHF by QSG might not completely is dependent on the improvement of cardiac pumping ability and cardiac structure.

Prolonging life and promoting QOL is the ultimate goal in the treatment of CHF [20]. Compared with the Minnesota Living with Hearth Failure Questionnaire (MLHFQ), the CHFQLS contains TCM contents, which is appropriate to China's national conditions and can better reflect the advantages and characteristics of TCM in preventing and treating CHF, and it has good reliability and validity [21]. Therefore, the CHFQLS was used to evaluate the QOL in CHF patients before and after treatment in this study. The results show that QSG could improve the total scores, physiological function, role limitation and vitality scores, enhance QOL of patients with CHF. This shows that holistic adjustment is the advantage of TCM in preventing and treating diseases.

The TCM syndrome score system is based on the TCM symptoms and signs, and is one of the most important and commonly used indexes to evaluate the efficacy of TCM in treating diseases [22]. Notably, statistical difference in TCM syndrome was observed between the QSG and TMZ group in this study. As common symptoms of CHF, shortness of breath, weakness and gasp are closely related to qi deficiency. The results of this study demonstrated that, compared with the TMZ group, QSG significantly improved the symptoms of qi deficiency (shortness of breath, weakness and gasp), which was the result of the intensive use of tonifying drugs. The fact that TMZ did not have similar effects illustrates the complexity of the TCM symptoms of qi deficiency. On the other hand, this finding also reflects the unique advantages of enriching qi treatment for improving the symptoms of qi deficiency. As CHF progresses, qi deficiency and blood stasis occur, which cause pulse stasis and decreased nourishment of qi and blood; the stagnation of qi and blood may lead to palpitations, chest tightness or chest and blood stasis syndrome. The movement of qi and blood is not smooth, and qi cannot exert its normal gasification function, resulting in the occurrence of water stagnation symptoms, such as general edema and abdominal distention. In this study, QSG significantly improved the symptoms of water stagnation (general edema), but there was no difference in the symptoms or signs of blood stasis (palpitations, chest tightness or chest pain and blood stasis syndrome). Approximately 73% of CHF patients included in this study had coronary heart disease as the basic disease. On the basis of full Western medicine treatment with QSG or TMZ, full use of Western medicine antiplatelet drugs may significantly improve blood stasis symptoms or signs in the two groups compared to those before treatment, so on this basis, TCM failed to show additional effects. Moreover, an increased follow-up time may reveal the benefits of TCM treatment.

Limitations Of The Study

Our study has several limitations. First, the sample size is small, which makes QSG show certain advantages in some outcomes in the treatment of CHF, but there were no significant differences between the two groups. Second, this study failed to assess long-term prognosis due to the limited observation period. In addition, due to the lack of quantitative indicators directly related to energy metabolism in this study, we are still unable to determine whether the improvement of qi deficiency symptoms is the same as the improvement of energy metabolism; this analysis requires further studies.
Conclusion

Our study illustrated that QSG were safe and efficacious in improving cardiac function, QOL, exercise tolerance, TCM syndrome, symptoms, signs, and NT-proBNP levels in patients with CHF class ì or î in stage C on the base of conventional treatment.

Abbreviations

ACEs, adverse cardiac events; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; ARs, Adverse reactions; CHF, chronic heart failure; CHFQLS, chronic heart failure integrated traditional Chinese and Western medicine survival scale; CHD1, coronary heart disease; CHD2, congenital heart disease; DCM, dilated cardiomyopathy; HHD, hypertensive heart disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; 6MWT, 6-minute walking test; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PHD, pulmonary heart disease; QSG, Qishentaohong granule; QOL, quality of Life; RHD, rheumatic heart disease; TCM, traditional Chinese medicine; TMZ, trimetazidine.

Declarations

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants provided written informed consent and the protocol was approved by the Ethics Committee of Dongfang Hospital Affiliated to Beijing University of Chinese Medicine (JDF-IRB-2017030402). The implementation of this study adhered to the guidelines of the Declaration of Helsinki and Tokyo for humans.

Consent for publication

Not applicable.

Conflicting interest

All authors declared that they had no confling interest.
Funding

This work was supported by the National Natural Science Foundation of China (grant number 81703902), Beijing Science and Technology Planning Project (CN) (grant number Z171100001017225) and Beijing University of Chinese Medicine 1166 Development Program for Junior Scientists (grant number 030903010331).

Authors' contributions

Yan Li and Qian Lin designed the experiment. Xing-xing Li drafted the manuscript. Zongjing Fan, Jie Cui, Quan Lin and Rong-kun Yan performed this experiment, and Xing-xing Li collected and analyzed the data. Yan Li and Yang Wu revised the manuscript. All authors reviewed and approved the final manuscript.

Acknowledgements

The authors are grateful to patients for participating in the present study and to our colleagues from the Department of Cardiology, Dongfang Hospital Affiliated to Beijing University of Chinese Medicine for their dedication, support, and hard work.

References

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56–28.

2. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ, CHARMM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur Heart J. 2008;29(11):1377–85.

3. Su JZ, Li LW, Lin Q. Lin Qian's Experience in Treating Chronic Heart Failure with Integrated Traditional Chinese and Western Medicine. Chin J Basic Med Tradit Chin Med. 2016;22(01):128–30.

4. Zhang Q, Li B, Xing DM, Wang YX, Zhu MJ. 2016. Discussion on the relationship between heart-qi deficiency syndrome and myocardial energy metabolism disorder in chronic heart failure. Chin J
5. Li Y. Effects of replenish qi on metabolism remodeling of myocardial energy in rat model of chronic heart failure. Beijing Univ Chin Med. 2012, 1–76.

6. Wu S, Chang G, Gao L, Jiang D, Wang L, Li G, Luo X, Qin S, Guo X, Zhang D. Trimetazidine protects against myocardial ischemia/reperfusion injury by inhibiting excessive autophagy. J Mol Med (Berl). 2018;96(8):791–806.

7. Zheng XY. Clinical research guidelines for new investigational drugs in traditional Chinese medicine. Beijing: China Medical Science Press; 2002. pp. 77–85. Beijing.

8. Wan J, Lin Q, Su JZ, Tan H, Li PH. Evaluation of standard validity of quality of life scale for chronic heart failure with integrated Chinese and western medicine. Chinese journal of integrated Chinese and western medicine,2016,36(11):1300–1303.

9. Xiang N. Clinical observation of Wenyang Yiqi Fang in treating chronic cardiac failure with deficiency of yang qi and blood stasis. Hubei Univ Chin Med.2019; 1–74.

10. He SL, Li YJ. Methodology of medical research. People's Mil Med Press. Appendix. Beijing. 2004; 601.

11. Wang H, Liang YC. 2018. Chinese Heart Failure Diagnosis and Treatment Guidelines 2018, Chin J. Cardiol. 2018; 46(10): 760–789.

12. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. JAMA. 2004;292(3):344–50.

13. Tsai MY, Hu WL, Lin CC, Lee YC, Chen SY, Hung YC, Chen YH. Prescription pattern of Chinese herbal products for heart failure in Taiwan: A population-based study. Int J Cardiol. 2017;228:90–6.

14. Li S, Nong Y, Gao Q, Liu J, Li Y, Cui X, Wan J, Lu J, Sun M, Wu Q, Shi X, Cui H, Liu W, Zhou M, Li L, Lin Q. Astragalus Granule Prevents Ca\(^{2+}\) Current Remodeling in Heart Failure by the Downregulation of CaMKII. Evid Based Complement Alternat Med. 2017; 2017:7517358.

15. Kim SW, Jang WS, Baek KM. Cardioprotective Effects of Salvia Miltiorrhiza Radix on the Pressure Overloaded Heart Failure Model by Transverse Aortic Constriction-induced Mice. The J Korean Med. 2016;37:23–35.

16. Liu Y, Ma W, Zhou W, Li L, Wang D, Li B, Wang S, Pan Y, Yan Y, Wang Z. The cytosolic protein GRP\(_1\) facilitates abscisic acid- and darkness-induced stomatal closure in Salvia miltiorrhiza. J Plant Physiol. 2020;245:153112.

17. Wei Y, Wu Y, Feng K, Zhao Y, Tao R, Xu H, Tang Y. Astragaloside IV inhibits cardiac fibrosis via miR-135a-TRPM\(_7\)-TGF-β/Smads pathway. J Ethnopharmacol. 2020;249:112404.

18. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah ND, Roger VL. Hospitalizations after heart failure diagnosis a community perspective. J Am Coll Cardiol. 2009;54(18):1695–702.

19. Bredy C, Ministeri M, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Diller GP, Gatzoulis MA, Dimopoulos K. New York Heart Association (NYHA) classification in adults with congenital heart
20. Xian SX, Yang ZQ, Ren PH, Ye XH, Ye SL, Wang QH, Wang ZH, Shen SJ, Huang XW. Effect of yangxinkang tablets on chronic heart failure: A multi-center randomized double-blind placebo-controlled trial. Chin J Integr Med. 2015;21(10):733–42.

21. Lin Q, Nong YB, Wan J, Lu JJ, Wen ZH, An C. 2008. A clinical study of scale for evaluating the quality of life in patients with chronic heart failure treated with traditional Chinese and western medicine. Chin J Integr Tradit West Med Intens Crit Care. 2008(3):131–134.

22. Wang XL, Mao JY, Hou YZ. Preliminary Study of Establishing Clinical Effect Evaluation Methods of Chinese Medicine Based on Combination of Disease and Syndrome, Systematic Staging, and Multi-dimension Index. Chin J Integr Tradit West Med. 2013;33(2):270–3.

**Figures**
Figure 1

Flow chart of the study Note: QSG, Qishentaohong Granule; TMZ, trimetazidine; ACEs, adverse cardiac events; ARs, Adverse reactions.
Figure 2

Comparison of the CHFQLS total scores and scores of each dimension between the two groups. Note: Values are expressed as mean ± SD. Change = 4-week level – baseline level *P<0.05, compared with the same group at baseline; △P<0.05, compared with the TMZ group at the same time-points.
| Characteristics                  | QSG                      | TMZ                      |
|---------------------------------|--------------------------|--------------------------|
|                                 | Baseline  | 4 Weeks | Reduction | Baseline  | 4 Weeks | Reduction |
| TCM syndrome score              | 20.17±5.18 | 8.80±4.96Δ | 11.37±5.25Δ | 20.23±4.14 | 12.66±5.11* | 7.57±4.47 |
| Symptoms or signs               |            |         |           |            |         |           |
| Shortness of breath             | 4.00±1.57  | 1.71±1.38Δ | 2.49±1.76  | 4.40±1.44  | 2.63±1.66* | 1.66±1.57 |
| Fatigue                         | 4.00±1.57  | 1.50±0.76Δ | 2.49±1.76  | 4.00±1.57  | 2.80±1.66* | 1.60±1.57 |
| Syndrome                          | 4-week level | Baseline level | Reduction | 4-week level | Baseline level | Reduction | 6MWT | NT-proBNP |
|----------------------------------|--------------|----------------|------------|--------------|----------------|------------|-------|-----------|
| Fatigue                          | 4.06±1.5*    | 1.5±1.2*       | △4.39±1.6/b | 4.40±1.46     | 2.80±1.69     | △1.60±1.3/ |      |           |
| Gasp                             | 1.69±0.87    | 0.51±0.56*     | 0.46±0.66Δ  | 1.34±0.76     | 0.97±0.79*    | 0.26±0.66  |      |           |
| Palpitation                      | 1.43±1.09    | 0.51±0.56*     | 0.91±1.09   | 1.00±0.77     | 0.54±0.66*    | 0.46±0.78  |      |           |
| Chest tightness or chest pain    | 3.00±1.78    | 1.46±1.59*     | 1.54±1.69   | 2.86±1.71     | 1.94±1.76*    | 0.94±1.59  |      |           |
| Blood stasis syndrome            | 3.43±1.80    | 2.14±1.89*     | 1.29±1.82   | 3.77±1.68     | 2.49±1.70*    | 1.29±1.82  |      |           |
| General edema                    | 1.80±0.83    | 0.57±0.61*     | 1.23±0.81Δ  | 1.80±0.83     | 0.97±0.71*    | 0.83±0.86  |      |           |
| Abdominal distention             | 0.77±0.69    | 0.31±0.53*     | 0.46±0.66   | 0.57±0.56     | 0.31±0.47*    | 0.26±0.66  |      |           |

**Figure 3**

Comparison of the TCM syndrome, symptom and sign scores between the two groups Note: Values are expressed as mean ± SD. Reduction=4-week level − baseline level. * P<0.05, compared with the same group at baseline; △P<0.05, compared with the TMZ group at the same time-points. 6MWT and NT-proBNP
Figure 4

Comparison of the 6MWT and NT-proBNP between the two groups Note: Values are expressed as mean ± SD. Reduction=baseline level – 4-week level; Change=4-week level – baseline level. *P<0.05, compared with the same group at baseline; △P<0.05, compared with the control group at the same time-points.