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Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Coronary Heart Disease Patients: Study Protocol for a Randomized Controlled Trial

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Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Coronary Heart Disease Patients: Study Protocol for a Randomized Controlled Trial

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Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Coronary Heart Disease Patients: Study Protocol for a Randomized Controlled Trial

INTRODUCTION: Preliminary evidence from clinical observations suggests that Tai Chi exercise may offer potential benefits for patients with coronary heart disease (CHD). However, the advantages for CHD patients to practice Tai Chi exercise as rehabilitation have not been rigorously tested and there is a lack of consensus on its benefits. This study aims to develop an innovative Tai Chi Cardiac Rehabilitation Program (TCCRP) for CHD patients and to assess the efficacy, safety and acceptability of the program.

METHODS AND ANALYSIS: We propose to conduct a multicenter randomized-controlled clinical trial comprising of 150 participants with CHD. The patients will be randomly assigned in a 1:1 ratio into either an intervention group or a control group. The intervention group will participate in a supervised TCCRP held 3 times a week for 3 months. The control group will receive supervised conventional exercise rehabilitation (CER) held 3 times a week for 3 months. After the 3-month intervention period, there will be a 3-month follow-up period with no active intervention in either group. The primary and secondary outcomes will be assessed at baseline, 1 month, 3 months and 6 months. Primary outcome measures will include a score of 36-Item Short Form Survey (SF-36) and Chinese Perceived Stress Scale (CPSS). The secondary outcome measures will include body composition, cardiopulmonary exercise test, respiratory muscle function, locomotor skills, echocardiogram, New York Heart Association (NYHA) classification, heart rate recovery time and laboratory examination. Other measures also include Seattle Angina Scale (SAQ), Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), Berg Balance Scale (BBS), Morse Fall Seale (MFS) and Kansas City Cardiomyopathy Questionnaire (KCCQ). All adverse events will be recorded and analyzed. Intention-to-treat analysis will be performed for participants who withdraw from the trial.

ETHICS AND DISSEMINATION: This study conforms to the principles of the Declaration of Helsinki and relevant ethical guidelines covering informed consent, confidentiality and data storage. Ethical approval has been obtained from the Ethics Committee of Chinese PLA General Hospital (approval number S2019-060-02).

All participants will be fully informed about the trial and will sign a consent form prior to participation. Findings from this study will be published and presented at conferences for widespread dissemination of the results.

Trial registration number: ClinicalTrials.gov identifier: NCT03936504

STRENGTHENS AND LIMITATIONS OF THE STUDY:

- TCCRP is specifically designed for patients with CHD.
- Tai Chi exercise is easily performed and mastered at home as a cost-free rehabilitation program.
- Gentle exercise for CHD patients encourages patient compliance.
- It is difficult to monitor any additional physical activity and accurately track daily activity intensity of participants.
- The blinding of participants is unachievable in this trial; however, efforts will be made to ensure that the data is blinded.

Keywords: Tai Chi, Coronary heart disease, Safety, Effectiveness, Randomized controlled trial, Exercise rehabilitation.

INTRODUCTION

Coronary heart disease (CHD) remains the major cause of morbidity and mortality worldwide. CHD responsible for about one in every seven deaths; and, CHS is predicted to continue until 2030, accounting for 14% of all deaths globally.[1,2] Despite the use of effective Western medicine treatments, the incidence of CHD continues to rise and is associated with a high mortality rate. While cardiac rehabilitation comprising contemporary exercises is recommended for CHD patients, over 60% of CHD patients

have been reported to decline current cardiac rehabilitation exercises as they perceive the physical exercise to be unpleasant, painful or impossible to perform in view of their conditions.[3] Consequently, there is an unmet need to develop an effective, yet feasible, alternative exercise therapy for CHD patients who don't participate in current cardiac rehabilitation exercises. Furthermore, an effective complementary is needed to be developed to improve the functional status and quality of life in CHD patients.

The integration of Traditional Chinese medicine (TCM) with Western medicine to treat CHD has made great progress. As an effective complementary therapy, TCM has been demonstrated to improve the prognosis of CHD patients.[4] Tai Chi is an important element of TCM which combines the meridians and collateral theory, Yin-Yang theory and Five-element theory. The coordinated movement of Tai Chi postures, namely "Stirring up Dantian", "Yi-Qi Cooperation", "Spiral Silk Reeling" and "Qi Flowing to Four Tips (hair, tongue, teeth and bone)" can promote the channeling of Qi and blood to nourish the body, resist diseases and promotes immunity. Previous studies have shown that regular Tai Chi exercise is beneficial in improving psychological and physiological outcomes among CHD patients.[3,5,6] A meta-analysis showed that Tai Chi exercise improves left ventricular ejection fraction (LVEF), cardiac output, stroke output and reduces resting myocardial oxygen consumption in elderly patients. In addition, Tai Chi improves vascular elasticity and promotes the regulation of blood pressure, glucose and lipids.[7]

However, there are many schools in Tai Chi such as the Yang-style, Wu-style, Chen-style, Wu-style and Sun-style, wherein each style takes a different approach in terms of the movements and forms. Furthermore, as Tai Chi exercise comprises many assorted movements that can be also complex to perform, it is difficult to popularize and simplify the exercise, especially in elderly patients and patients with chronic diseases.

Based on prior insights of the Tai Chi movements obtained from our studies and other published work,[8,9] our research team developed an innovative TCCRP specifically for CHD patients. However, as the value of TCCRP has yet to be clinically proven, a clinical trial is required to validate the benefits of adopting this exercise for CHD patients.

This study aims to assess the efficacy, safety, and acceptability of TCCRP for CHD patients. The primary hypothesis is that TCCRP (the intervention group) will improve 36-Item Short Form Survey (SF-36), and reduce the score of Chinese Perceived Stress Scale (CPSS) when compared against conventional exercise rehabilitation (CER, the control group). Secondary objectives are to evaluate the effects of the TCCRP on body composition, cardiopulmonary exercise test, respiratory muscle function, locomotor skills, echocardiogram, NYHA classification, heart rate recovery time and laboratory examination. Other indicators measured will include SAQ, PSQI, PHQ-9, GAD-7, BBS, MFS, KCCQ and major adverse cardiac events. Additional objectives to be explored will include: (1) the influence of potential factors on the adherence to the TCCRP; (2) the safety of the TCCRP and (3) individual experiences and acceptability following the TCCRP.

Methods/Design

Study design

This is a prospective, multicenter, randomized-controlled clinical trial comparing a TCCRP with CER with an allocation ratio of 1:1. The study period lasts for 6 months including a 3-month supervised intervention and a 3-month follow-up with the primary outcomes measured at baseline, 1 month, 3 months and 6 months. Secondary outcomes will be measured at baseline and after a 3-month intervention period.

This study is registered on ClinicalTrial.gov (NCT03936504). A brief flowchart of the entire study is shown in Figure 1 and the schedule of events is provided in Table 1.

Participants

Inclusion criteria

1. Male or non-pregnant women aged from 18 to 80 years;
2. Patients who met the criteria for stable angina pectoris in accordance with CHD classifications;
3. NYHA class I, Π or ΙΙΙ; and
4. Participants who understood the purpose of the clinical trial and voluntarily participate with signed informed consent.

Exclusion criteria

1. Acute myocardial infarction (AMI) within 2 weeks;
2. Severe aortic stenosis;
3. Hypertrophic cardiomyopathy;
4. Severe valvular heart disease;
5. Malignant tachyarrhythmia;
6. Poor patient compliance and incompletion of the clinical trial for not satisfying the requirements;
7. Patients with nervous system deterioration, motor system disease, or rheumatic disease caused by combined exercise;
8. Those who regularly practice Tai Chi during the previous 3 months.

Setting and Recruitment

This multicenter study will be performed at the Beijing Normal University in China. Recruitment and exercise training will occur at the Chinese PLA General Hospital, China, Beijing Shuili Hospital, China, and Anzhen Community Health Service Center, Beijing Chaoyang District, China. One hundred and fifty participants are to be recruited and the recruitment is scheduled to begin in October 2019. Combinations of advertising strategies include flyers within the hospital, advertisements in the print, online media, a major messaging platform (WeChat), clinics and databases.

Randomization, allocation concealment and blinding

After informed consent is signed, all patients will be randomized into either an intervention group receiving a 12-week TCCRP or a control group receiving CER. The random allocation sequence will be produced by an independent statistician via the PLAN sentences of the statistical software SAS 9.2 in a 1:1 ratio. Next, these assignments will be sent to a study staff member, exclusive to the study coordinator or principal investigator, who will store them into sealed, opaque envelopes with date and signature labels placed over the seals of the envelopes. The randomization envelopes

will not be opened unless a participant meets eligibility criteria, completes the informed consent, and undergoes a baseline assessment. The study is conducted in 3 different cycles. Each cycle consists of a TCCRP group (intervention group) and CER group (control group). Each resulting group consists of 25 patients, equating to a 50 patients participating in each cycle, with a total of 150 patients over the course of the 3 cycles comprising the study. The instructors are randomly assigned to the 3 cycles.

Given the nature of the intervention, it is impossible to blind the patients or any personnel who are directly involved in conducting the programs. However, all outcome assessors, laboratory technicians, data managers and statisticians will be kept blind of the treatment allocations.

Patient and Public Involvement

Involvement of patients and public help us to recognize whether we are doing the right thing. Moreover, our research is investigating the impact of different exercise types, while irrelevant to any drug or pharmacy corporations, so we can give priority to patients as far as possible. During the clinical work of cardiac rehabilitation (CR) exercise training, we always take a lot of time to communicate with patients to ask about their opinion about coronary artery disease, and about life style therapy and exercise training. The patients discussed many times with me whether we could practice the Chinese traditional Qigong, such as Baduanjin or TaiChi. Compared with generally accepted aerobic exercise, dose TaiChi exhibit better effect? There are few well designed clinical trials which could answer the question, so we chose this study to perform.

Since the very beginning of our study, we have constructed a Patient Public Involvement group, to let us know what are the things patients think to be most important and whether we have done the right study. We choose on purpose the CHD patients with different work and different income level. For example, we chose government officials, workers, cook, information technology programmer and teachers. We held several group meetings, to discuss with them what are the things troubling them most now, what do they think about exercise training and TaiChi, and what is the

most effective aspect do they think TaiChi would work. We also ask them whether they worry about the safety of exercise, and which kind of exercise do they think is the safest. Many patients told us they had heard TaiChi could improve the sleeping disorder and insomnia. After the discussion were held, we realized CHD patients care most about how much physical activity is limited, and how to reduce the incidence of angina pectoris. Besides, they are willing to try some Chinese traditional Qigong, such as Baduanjin or Taichi. So we designed our study to compare the impact of TaiChi and traditional exercise training among CHD population. Taken into consideration of what the patients care most, to take patients' priorities and preferences, we chose the improvement of cardiopulmonary capacity, score of 36-Item Short Form Survey (SF-36) ,sleep quality index and score indicating stress as outcomes.

We have constructed a Patient Public Involvement group and held the group meeting periodically. We discussed with the patients to find out the most important aspect they care to be investigated. They also helped us recognize the valuable outcomes to be measured. We also contact with them during the conducting period of study to find the most effective and convenient way for patients. For the sake of patients, we also perform the study at the hospitals, a location familiar to participants.

Patients were involved a lot in the recruitment to and conduct of the study. During the group meeting, Patient Public Involvement group members were informed about how the study will be conducted. We also discussed the issue about participant recruitment in detail. After the communication, the patients suggested us to prepare simple booklet to introduce our study during the outpatients visit and by internet, also to enlarge the recruitment extent by WeChat and app of our hospital through smart mobile phone. The possible difficulties in recruitment were also assessed by the research team and Patient Public Involvement group members together. The possible methods were also to be mined.

The detailed training schedules were also discussed with the group members in order to determine the data and time convenient for the patients. Based on the suggestion by the patient and public involvement group members, we used ECG monitoring during the exercise training. During the study, the patient and public involvement group

members were asked periodically if they felt comfortable and able to continue participating. During the study, Patient Public Involvement group members also feedback with us whether and when we should extend the rest time. Patient Public Involvement group members also helped us explain to the patients what our study is about and the detail of the study in the way patients can understand easier.

We planed to disseminate our research to the participants and the public, such as publicizing our research in hospital official accounts and various academic lectures. At the same time, we also recommend that patients in the group send study results to their respective friend WeChat groups and family WeChat groups to spread the results rapidly. We discussed the way to disseminate findings to study participants with Patient Public Involvement group. They suggested us share the results to all the participants face to face. By this way, the study researchers could explain the results more clearly and instruct them to choose the more effective exercise type.

They have been informed on detail, and it will be the patients themselves who decides whether to take part in or not. We also discussed the study protocol with Patient Public Involvement group members. Randomised trial means no one could decide which intervention will be delivered to a certain patient. Patient Public Involvement group suggested we can teach the participants in control group Tai Chi for free, later after they have finished the total study if they want. This will be more grateful for those who longs for be randomized to Taichi group. Patient advisers should also be thanked in the contributorship statement/acknowledgements. Finally, to measure the burden more clearly, we will also ask them to fill in a scale to tell more details about the burden of the intervention.

In the end, we have added the acknowledgements to Patient Public Involvement group members for their support for this study.

INTERVENTIONS

Tai Chi cardiac rehabilitation program (TCCRP) group

Patients in the intervention group will receive TCCRP conducted by a cardiac rehabilitation team consisting of cardiologists, cardiology nurses, Tai Chi coaches and

research assistants. Procedures and activities of the TCCRP include: (1) Tai Chi exercise, (2) evaluation of exercise ability, (3) education covering topics related to the exercise, and (4) a series of adherence strategies.

TCCRP pre-phase: a 2-week exercise before the start of exercise

1. TCCRP training

Three professional coaches with at least 5 years of Tai Chi teaching experience will be employed to teach and guide the participants' training. TCCRP will include (a) traditional Tai Chi warm-up exercises, followed by (b) Bafa Wubu of Tai Chi, (c)Tai Chi elastic belt exercise and (d) Tai Chi cool-down exercises.

(a) Tai Chi warm-up exercises (10 minutes) will include traditional breathing methods (full-body breathing), weight shifting, arm-swinging etc. These exercises will help release tension in the physical body, incorporate mindfulness and imagery into movement, increase breathing awareness and promote overall relaxation of the body and mind.

(b) The core Tai Chi movements (30 minutes) will be adapted from the Bafa Wubu of Tai Chi (also known as "eight methods and five footwork", Fig. 2), which include introductory routines to Tai Chi characterized with simple structures and rich connotations performed repetitively. Technically speaking, the "Bafa" consists eight hand techniques, namely "Peng (warding off), Lu (rolling back), Ji (pressing), An (pushing), Cai (pulling down), Lie (splitting), Zhou (elbowing) and Kao (shouldering)"; while the "Wubu" consists five footwork, namely "Jin (advancement), Tui (retreat), Gu (shifting left), Pan (shifting right) and Ding (central equilibrium).

(c) Tai Chi combined with light-weight resistance band exercises(10 minutes) will include Tai Chi "Open and Close" movement, Tai Chi Spinning movement and Tai Chi Twining movement.

(d) Tai Chi cool-down exercises (10 minutes) will include various relaxation methods, such as regulating breathing, regulating Qi and regulating mindfullness (Yi).Patients are required to practice the TCCRP until they master it. Mastery will be determined by the professional coaches.

2. Evaluation of exercise ability (week − 1 to week 0):

(a) Evaluation is conducted by cardiologists and physiotherapists;

(b) Evaluation is based on reviewing medical history, cardiopulmonary exercise test results and the performance of Tai Chi (heart rate and oxygen consumption will be recorded while performing Tai Chi);

(c) Evaluation results will guide the goal-setting process during consultation;

3. Education covering topics related to exercise:

(a) Basic knowledge of chronic heart disease,

(b) Basic knowledge of exercise-based cardiac rehabilitation.

TCCRP exercise phase: a 12-week intervention period

Participants will perform the TCCRP 3 times a week for 12 weeks. Each training session is 60 minutes and includes Tai Chi warm-up exercises (10 minutes), Bafa Wubu of Tai Chi (30 minutes), Tai Chi combined with light-weight resistance band exercises (10 minutes) and Tai Chi cool-down exercises (10 minutes). All participants will be encouraged to practice Tai Chi according to an instructional video until the end of the 12-week period.

Researchers will record the subjects' heart rate and blood pressure before and after training. During the training, the exercise intensity will be assessed by the Borg Rating of Perceived Exertion Scale (RPE Scale),[10] which is a frequently used quantitative measure of perceived exertion during exercise.

TCCRP follow-up phase: a 12-weeek follow-up period

After the 12-week TCCRP intervention, there will be a 12-week follow-up period that excludes any active rehabilitation. During the follow-up period, the participants will be asked to fill out forms to record the times and durations of their Tai Chi exercise or other physical activities and any incidence of a major adverse cardiac event. The forms will be returned to the researchers for follow-up each week by email or WeChat.

CER group (Control group)

Participants in the control group will receive a CER 3 times a week for 12 weeks. Each training session lasts for 60 minutes, including ordinary warm-up exercises (10 minutes), aerobic activity (30 minutes), resistive exercise (10 minutes) and cool-down exercises (10 minutes). Each training session includes: (1) an active warm-up including arm-swinging, gentle stretches of the neck, shoulders, spine, arms and legs; (2) an aerobic activity comprising primarily cycle ergometer exercise; (3) resistive exercise mainly including resistance band exercises; and (4) a cool-down session involving active and static stretching exercises with primary body movements.

The CER program is consistent with the current recommended guidelines of moderate intensity exercises (50 to 80% Heart Rate Reserve (HRR): Rated Perceived Exertion 11–13) for CHD patients**.** Our program is individually tailored to each participant alongside close supervision. The program will be introduced and increased in duration and intensity gradually to achieve the target of moderate-intensity exercise.

Concomitant treatment

Participants in both groups will continue routine medications, such as aspirin, metoprolol, anti-platelet and anti-coagulant drugs or beta-adrenergic blockers, according to patients' respective conditions and will maintain their usual treatment visits throughout the study. All procedures and medication prescriptions will be determined by physicians following the clinical guidelines.[11,12] The specific date and reasons of any medical therapy changes will be recorded in the case report form (CRF).

Outcome measures

All outcome measures will be collected by 3 research assistants at 2 weeks (baseline), 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up). Demographic information collected will include age, gender, ethnicity, marital status, education level, accommodation type and postal address. Clinical information will also be obtained from the patients' clinical records by a member of their hospital research team. All data collected from the assistants and therapists will be stored in a

dedicated computer for the study and will be kept in a secure and lock-protected location.

Primary outcome measures

1. The SF-36 Health Survey (SF-36) is a multi-purpose, short-form health survey with only 36 questions.[13] SF-36 items cover eight domains: physical functioning, role limitations due to physical health problems, body pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. Higher scores indicate higher levels of health. SF-36 will be evaluated at baseline, 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up).
2. Chinese Perceived Stress Scale (CPSS) is a self-rated questionnaire that assesses perceived stress.[14] CPSS consists 14 items that are divided into two categories: sense of tension and loss of control. Higher scores indicate higher levels of stress. CPSS will be evaluated at baseline, 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up).

Secondary outcome measures

1. Body composition measurements will include fat mass, body fat (percentage), fat-free mass and lean body mass. These measurements will be taken by bioelectrical impedance analysis using an Inbody 770 (Biospace Co) at baseline, 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up).
2. Cardiopulmonary exercise test (CPET) is an objective method being increasingly used in a wide spectrum of clinical practice for assessing the functional capacity of CHD patients. Indexes include changes in VO_2 peak and VAT and VE/ VCO_2 slope in the cardiopulmonary exercise test (CPET) at the end of the 3-month intervention.
3. Respiratory muscle function will be measured by POWER breath K-5. Indexes include changes in S-Index, Peak PIF of inspiratory velocity and power at the end of the 3-month intervention.
4. Locomotor skills includes handgrip strength, balance and flexibility. Handgrip

strength, which is used to determine the maximum isometric strength of the hand and forearm muscles, will be measured using the handgrip strength dynamometer produced by CAMRY (product type EH101). The best result from repeated tests of each hand will be recorded. The balance test mainly includes standing on one foot with eyes closed, standing on one foot with eyes open, standing in situ with closed eyes and so on. Flexibility will be measured by seated forward flexion test. Locomotor skills will be evaluated at baseline and at the end of the 3-month intervention.

5. An echocardiogram comprising LVED Vi and LVEF using echocardiography will be assessed at baseline and at the end of the 3-month intervention. NYHA classification will also be evaluated at baseline and at the end of the 3-month intervention.
6. Heart rate recovery time will be measured. Heart rate recovery time will record heart rate 1 to 6 minutes after Tai Chi exercise, power cycling and resistance exercise.
7. A laboratory examination will be performed that includes glycolipid metabolism, inflammatory factor level, immunologic function and oxidative stress index. The laboratory examination will be evaluated at baseline and at the end of the 3-month intervention.
8. The Berg Balance Scale (BBS) is a widely used clinical test of a person's static and dynamic balance abilities,[15] and comprises of a set of 14 simple balance related tasks, ranging from standing up from a sitting position to standing on one foot. Total score ranges from 0 to 56, with 0 to 20 corresponding to a high fall risk, 21 to 40 a medium fall risk and 41 to 56 a low fall risk. The Berg Balance Scale will be evaluated at baseline and at the end of the 3-month intervention.
9. The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire that assesses sleep quality and disturbances.[16] It contains 19 self-answered questions for the subject and 5 peer-answered questions for the bed partner or a roommate (if one is available). The scores from seven categories are added to calculate the index, ranging from 0 to 21. A score of zero indicates no disturbance in sleep or good

sleep quality, whereas higher scores indicate poorer sleep quality. The PSQI will be evaluated at baseline and at the end of the 3-month intervention.

10. Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7(GAD-7) are validated self-answered questionnaires that assess levels of depression and anxiety. Higher scores reflect greater levels of anxiety and depression. PHQ-9 and GAD-7 will be evaluated at baseline and at the end of the 3-month intervention.
11. The Seattle Angina Score (SAQ) will be used to determine the total number of 9 problems and the 5 aspects of CAD, including the degree of physical activity, the stability and frequency of angina, the degree of satisfaction of the treatment, and the perception of the disease. The higher the score, the better the quality of life and body function. SAQ will be measured at baseline and at the end of the 3-month intervention.
12. A record will be made of any side effects and possible adverse reactions arising from the intervention.

Safety measurements

All study participants are monitored weekly during the study intervention for the occurrence of adverse events defined by any undesirable experience. All adverse events that occur during the study will be recorded on the Adverse Event Case Report Form and will be evaluated for relevance to the intervention. All adverse events will also be reported to the Human Research Committee promptly in accordance with guidelines.

Only patients who are eligible and capable of completing the test will undergo a Cardiopulmonary Exercise Test (CPET). For enrolled patients meeting the rehabilitation training standards, they will be stratified according to the degree of motion risk and appropriate exercise intensity and time will be adjusted based on their risk stratification. Before the cardiac rehabilitation exercise, researchers will educate patients about the CHD rehabilitation exercises, including training contraindications and exercise advisories regarding the respective CER and TCCRP exercises. Moreover, the cardiac rehabilitation Center of Chinese PLA General Hospital, Beijing Shuili

Hospital and Anzhen Community Health Service Center are equipped with a comprehensive set of rescue equipment. A thorough contingency plan and rescue procedure for cardiovascular events has also been formulated prior to the commencement of the research. Should an adverse event occur during the exercise, the researchers will immediately initiate the contingency plan to circumvent the occurrence of any fatal outcomes.

Data management and monitoring

Beijing Normal University will be responsible for monitoring research progress, managing the data and performing statistical analyses. The research assistants will be responsible for checking the integrity of the completed CRF and for timely entry of the collected data into the EpiData Manager, a free data management software. The project manager will be responsible for initial data cleaning, identifying, coding and converting the data into the proper format for analysis. All investigators involved in data management and analysis will be blinded to treatment allocation.

Statistical analysis

Continuous variables will be presented as the mean ± standard deviation (SD). Median or interquartile range (IQR) and categorical variables will be presented as frequencies or percentages. Baseline data between the two groups will be compared and assessed using a two-sample Student's t-test for continuous variables and the chi-square test or Wilcoxon test for categorical variables. Questionnaire score data, also known as non-normally distributed data, will be transformed and analyzed with a nonparametric test. We will conduct an intention-to-treat analysis if participants are lost or dropout from the study prior to the follow-up. All data will be analyzed with SPSS 21.0 (IBM, Chicago, IL, USA) software packages and Microsoft Excel 2007. Statistical significance is defined as a two-sided P value < 0.05.

Adherence

During the 3-month treatment period, participants will be asked to practice strictly

according to the training program and will not be allowed to take part in any new or additional exercise programs. Throughout the 3-month intervention period, the researchers will track the number of missed sessions for each participant during the intervention period. Participants' attendance will be monitored during each in-person session by staff-completed attendance forms and class sign-in sheets. The percentage of compliance will be documented on the case report form. The rate of patient compliance = (total planned number of times − number of absence) / total number of times × 100%. A compliance rate of 80% or greater will be considered as good, whereas a compliance rate of less than 80% is considered as poor. An attendance of less than 20% will be considered as a dropout from the study.

Discussion

The development of an ideal and effective cardiac rehabilitation program is still being explored and current cardiac rehabilitation mainly consists of contemporary cardio exercises. In fact, current cardiac rehabilitation programs have been reported to be underdeveloped and limited, reflected by a poor level of involvement with less than 30% of patients participating in the existing offerings.[17] As such, there is an unmet need for reforms and the provision of alternative cardiac rehabilitation programs to encourage the growth of cardiac rehabilitation. The exploration of an ideal cardiac rehabilitation exercise that is most beneficial for CHD patients should be determined by its complementary effects to the efficacy of existing treatments.

This trial will be the first to compare the feasibility, safety and benefits of TCCRP and CER in CHD patients. Compared with conventional exercise styles (e.g. aerobic, resistance, and extensibility exercise), Tai Chi typically involves a mind–body integration practice that balances the Yin and Yang in the body, promotes blood circulation and Qi for maximizing both physical and mental well-being.[18-20] Previous studies have shown that regular Tai Chi exercise is beneficial in improving psychological and physiological outcomes among the elderly and various clinical populations (e.g. Parkinson's disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD) and psychological illness).[21-24] As a typical

mind–body exercise which incorporates the characteristics of Traditional Chinese Medicine, Tai Chi may be considered to be an effective exercise to promote health in a diverse range of populations (e.g. healthy population, patients with chronic diseases, youths, middle-aged or elderly adults) [7,25,26,].

At present, many Tai Chi intervention programs differ diversely in terms of their duration, style and movements. In fact, some Tai Chi styles and movements can be too complex or difficult for older people to learn; and thus, not all Tai Chi styles and movements are suitable for patients with CHD. Hence, our research team developed a simple and gentle TCCRP that is especially suitable for patients with CHD, whose activity tolerance is poor.

An earlier study reported that over 60% of CHD patients would decline the regular cardiac rehabilitation exercise if they perceived the physical exercise to be unpleasant, painful or impossible to perform in view of their conditions.[3] In that study, CHD patients who declined the regular cardiac rehabilitation, underwent a Tai Chi exercise program and were found to be very receptive of the Tai Chi exercise (66% compliance rate). In fact, all patients who experienced the Tai Chi rehabilitation program shared that they will recommend it to a friend, thereby suggesting a high level of acceptance of Tai Chi as a cardiac rehabilitation exercise for patients. Corresponding to the objectives of the current proposed study, the previous study by Salmorirago-Blocthcer et al. concluded that it is imperative to validate the benefits of Tai Chi in a larger cohort of CHD patients in order to develop Tai Chi as an ideal alternative cardiac rehabilitation exercise.[3]

There are several strengths of our trial: 1) the proposed research study is unique in that the TCCRP is specifically designed for patients with CHD; 2) Tai Chi exercise can be easily performed and mastered at home and is relatively gentle for CHD patients to practice thereby encouraging patient compliance. Moreover, if the TCCRP is proved to be effective, TCCRP can be a high compliance and cost-free rehabilitation program that patients can do at home. This will help save time and costs for CHD patients requiring cardiac rehabilitation while potentially reducing social medical expenditure.

It should be acknowledged that this study has several limitations. It is difficult to

monitor any additional physical activity of participants during the study duration. Although all participants will be required to record their daily physical activity or exercise information with a pedometer, this is not sufficiently accurate to track their daily activity intensity. Furthermore, due to the nature of the exercise interventions (Tai Chi versus CER), the blinding of participants is unachievable in this trial. However, every effort will be made to ensure that the outcome assessors, data managers and statisticians participating in this study will be kept blind of the treatment allocations.

In conclusion, this study aims to develop an effective TCCRP for CHD patients and to explore the safety and effectiveness of TCCRP intervention in CHD patients. The results obtained from this trial will be vital to help establish an optimal cardiac rehabilitation program for treating CHD patients and will provide reliable evidence for the potential application of TCCRP in cardiac rehabilitation. Lastly, the findings from this study will also provide relevant understanding for developing a Chinese Tai Chi rehabilitation guide to complement existing CHD therapies.

Trial status

This trial began to recruit patients from October 2019. Estimated completion of the trial is expected to be completed by December 2020.

Additional files

Abbreviations

CHD: coronary heart disease; TCCRP: Tai Chi cardiac rehabilitation program; TCM: Traditional Chinese Medicine; CER: conventional exercise rehabilitation.

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Authors' contributions

MJ, LSJ and YHC conceived and designed the study protocol. The individual interviews were conducted by MJ, LH, ZLS, and GAY. MJ and ZJW performed the translation and analysed the data. ZJW, YW, CZH, WQY, CMZ, LYM, LYL, GTM, LCH, SB and WHW guided and supervised the Tai Chi training. MJ and ZJW contributed to writing and reading the manuscript. All authors approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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i

Table 1: Schedule for data collection; outcome measures per visits

Items	Phase I: Screening	Phase II: Baseline	Phase III: Month 1	Phase IV: Month 3	Phase V: Month 6
Inclusion/exclusion criteria	√				
Diagnostic index	√				
Signed informed consent	√				
Randomization and allocation	√				
Safety index	√	√	√	√	
General clinical information		√		√	
Primary outcomes		√		√	
Secondary outcomes		√		√	
Other indicators		√		√	
Recurrent cardiovascular events			√	√	√
Adherence			√	√	√
Adverse events			√	√	
Summary at the end of the study					√

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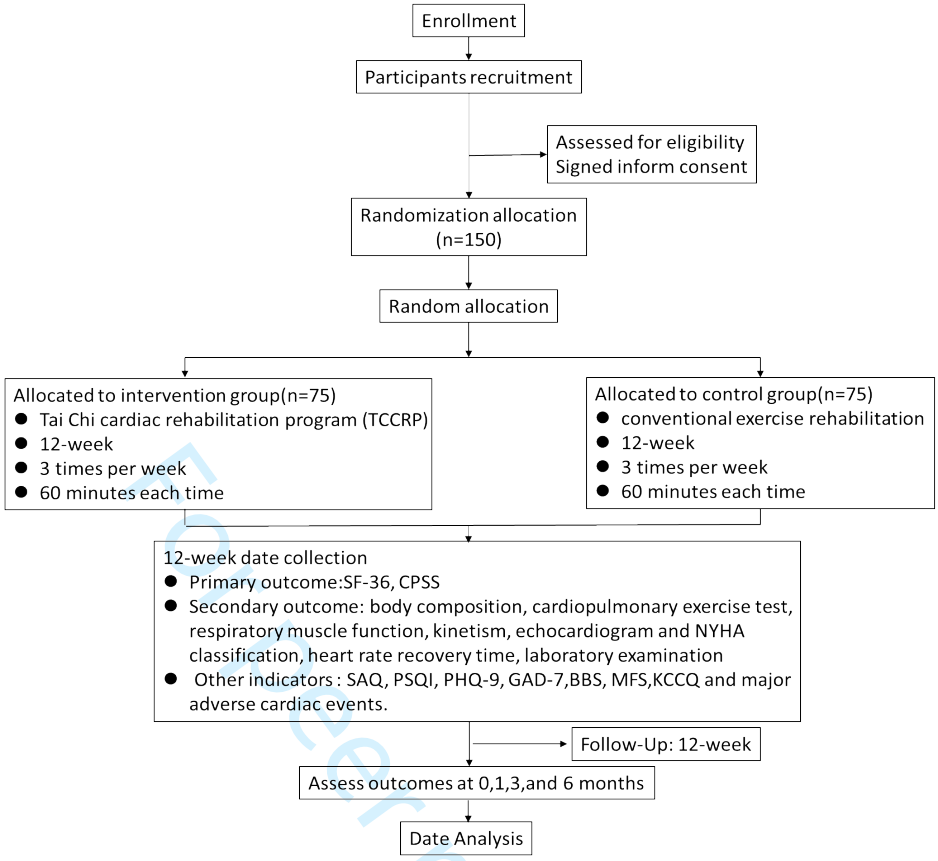

Figure 1: Flow diagram of study design

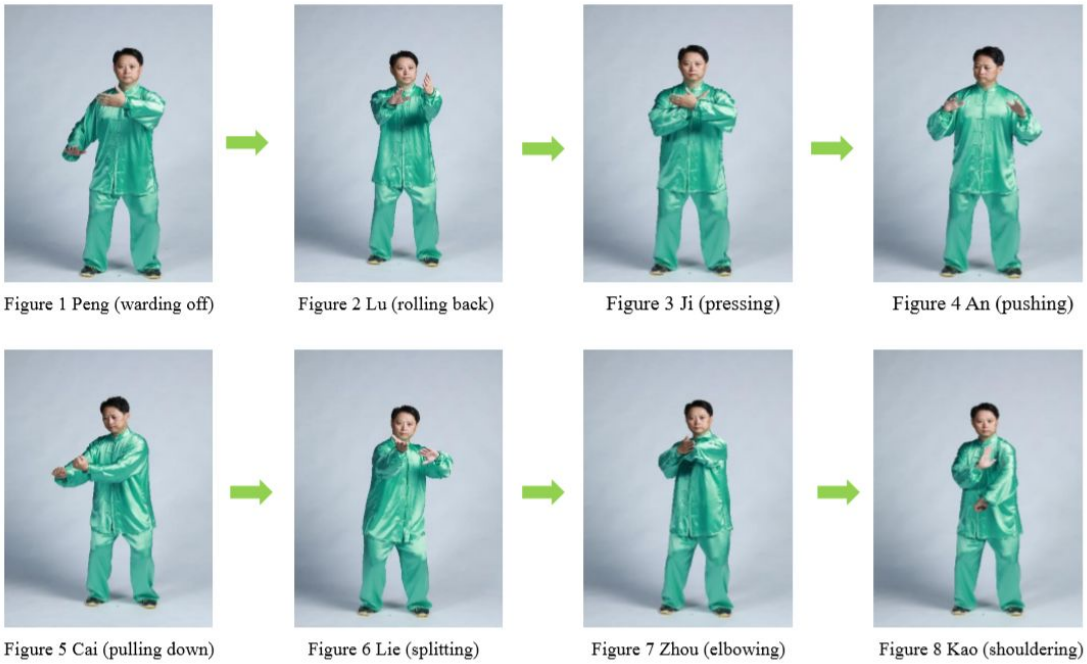

Figure. 2: Exemplary Bafa Wubu of Tai Chi; the pictures have taken the portrait right; the fugleman is the developer of TCCRP.

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Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Chronic Coronary Syndrom Patients: Study Protocol for a Randomized Controlled Trial

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Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Chronic Coronary Syndrom Patients: Study Protocol for a Randomized Controlled Trial

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Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Chronic Coronary Syndrom Patients: Study Protocol for a Randomized Controlled Trial

ABSTRACT

Introduction: Preliminary evidence from clinical observations suggests that Tai Chi exercise may offer potential benefits for patients with chronic coronary syndrom(CCS). However, the advantages for CCS patients to practice Tai Chi exercise as rehabilitation have not been rigorously tested and there is a lack of consensus on its benefits. This study aims to develop an innovative Tai Chi Cardiac Rehabilitation Program (TCCRP) for CCS patients and to assess the efficacy, safety and acceptability of the program.

Methods and analysis: We propose to conduct a multicenter randomized-controlled clinical trial comprising of 150 participants with CCS. The patients will be randomly assigned in a 1:1 ratio into two groups. The intervention group will participate in a supervised TCCRP held 3 times a week for 3 months. The control group will receive supervised conventional exercise rehabilitation (CER) held 3 times a week for 3 months. The primary and secondary outcomes will be assessed at baseline, 1 month, 3 months after intervention and after an additional 3 months follow-up period. Primary outcome measures will include a score of 36-Item Short Form Survey and Chinese Perceived Stress Scale. The secondary outcome measures will include body composition, cardiopulmonary exercise test, respiratory muscle function, locomotor skills, echocardiogram, New York Heart Association classification, heart rate recovery time and laboratory examination. Other measures also include Seattle Angina Scale, Pittsburgh Sleep Quality Index, Patient Health Questionnaire-9, Generalized Anxiety Disorder-7 and Berg Balance Scale. All adverse events will be recorded and analyzed.

Ethics and dissemination: This study conforms to the principles of the Declaration of Helsinki and relevant ethical guidelines. Ethical approval has been obtained from the Ethics Committee of Chinese PLA General Hospital (approval number S2019-060-02). Findings from this study will be published and presented at conferences for widespread dissemination of the results.

Trial registration number: ClinicalTrials.gov identifier: NCT03936504

Strengths and limitations of this study:

- The proposed research study is unique and the first study about a Bafa Wubu of Tai Chi which is a new Tai Chi school.
- TCCRP in this study was specifically designed for patients with CCS.
- This is the first time for Tai Chi study to develop a comparative training system to match the conventional exercise.
- It is difficult to exclude the effect of other physical activity due to difficulty of monitoring.
- The blinding of participants is unachievable in this trial; however, efforts will be made to ensure that the data is blinded.

Keywords: Tai Chi, Coronary heart disease, Chronic coronary syndrom, Safety, Effectiveness, Randomized controlled trial, Exercise rehabilitation.

INTRODUCTION

Coronary heart disease (CHD) remains the major cause of morbidity and mortality worldwide. CHD responsible for about one in every seven deaths; and, China Heart Society is predicted to continue until 2030, accounting for 14% of all deaths globally.[1] [2] Despite the use of effective Western medicine treatments, the incidence of CHD continues to rise and is associated with a high mortality rate. Cardiac rehabilitation (CR), especially exercise training is proven to significantly alleviate the cardiac symptoms, preserve the heart function, and improve the clinical outcomes. Therefore cardiac rehabilitation is recommended by many guidelines of different countries.[3-9] However, latest study demonstrated only 24.4% CR-eligible Medicare beneficiaries participated in CR and marked disparities were observed.[10] Besides limitation of medical resource, poor compliance of patients remains main reason. An effective and attractive CR training system is urgently needed.

These years the integration of Traditional Chinese medicine (TCM) with Western medicine to treat CHD has made great progress. As an effective complementary therapy, TCM has been demonstrated to improve the prognosis of CHD patients.[11] Tai Chi is an

important element of TCM which combines the meridians and collateral theory, Yin-Yang theory and Five-element theory. Tai Chi exercise contains three core elements, namely "body", "breath" and "mind", as pronounced in Chinese as "Xing", "Qi", "Yi" respectively. The spirits of Tai Chi are summarized to "building the body", "conveying the breath" and "using the mind". Previous studies have shown that regular Tai Chi exercise was beneficial in improving psychological and physiological outcomes among CHD patients.[12-15] Study by Professor Salmorirago-Blocthcer have showed patients receiving Tai Chi exercise exhibited much better compliance than those receiving conventional exercise. [12]

There are many schools in Tai Chi such as the Yang-style, Wu-style, Chen-style, Wu-style and Sun-style, wherein each style takes a different approach in terms of the movements and forms. Furthermore, as Tai Chi exercise comprises many assorted movements that can be also complex to perform, it is difficult to popularize and simplify the exercise, especially in elderly patients and patients with chronic diseases.

Based on prior insights of the Tai Chi movements obtained from our studies and other work,[16] [17] our research team developed an innovative Tai Chi Cardiac Rehabilitation Program (TCCRP) specifically for CHD patients. However, as the value of TCCRP has not yet to be clinically proven, a clinical trial is required to validate the benefits of adopting this exercise for CHD patients.

CHD can be categorized as either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) due to pathophysiological features and clinical prognosis because it is dynamic process of atherosclerotic plaque accumulation and functional alterations of coronary circulation[18]. Between the two process, most CHD patients stay in the CCS state. Latest studies revealed patients with CCS benefit a lot from cardiac rehabilitation programs characterized by life style therapy[18]. So we chose CCS patients as our subjects. This study aims to assess the efficacy, safety, and acceptability of TCCRP for CCS patients.

The primary hypothesis is that TCCRP (the intervention group) will improve the life quality and reduce the stress when compared against conventional exercise rehabilitation (CER, the control group). Secondary objectives are to evaluate the effects

of the TCCRP on body composition, cardiopulmonary exercise test, respiratory muscle function, locomotor skills, echocardiogram, New York Heart Association (NYHA) classification, heart rate recovery time and laboratory examination. Other indicators measured will include Seattle Angina Scale (SAQ), Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), Berg Balance Scale (BBS) and major adverse cardiac events. Additional objectives to be explored will include: (1) the influence of potential factors on the adherence to the TCCRP; (2) the safety of the TCCRP and (3) individual experiences and acceptability following the TCCRP.

METHODS/DESIGN

Study design

This is a prospective, multicenter, randomized-controlled clinical trial comparing a TCCRP with CER with an allocation ratio of 1:1. The study period lasts for 6 months including a 3-month supervised intervention and a 3-month follow-up with the primary outcomes measured at baseline, 1 month, 3 months and 6 months. Secondary outcomes will be measured at baseline and after a 3-month intervention period.

This study is registered on ClinicalTrial.gov (NCT03936504). A brief flowchart of the entire study is shown in Figure 1 and the schedule of events is provided in Table 1.

Sample size calculation

Sample size calculation will be based on the co-primary outcomes of the RCT. The SF-36 Health Survey (SF-36) and Chinese Perceived Stress Scale (CPSS) are being set as the co-primary outcome and used for sample size calculation. Sample size was calculated on the basis of the changes in the SF-36 and CPSS between comparison groups with a significance level of 5% and a two-tailed critical region to ensure the same effect size with 80% power by G*power V.3.1.9.4 software. The means and their SDs (mean ±SD) of the SF-36 and CPSS in the control and intervention group were (64.30±13.11, 71.79±16.03)[19] and (42.31±8.17, 35.15±6.82)[20], respectively, at

postintervention according to the published literature. Because the sample size calculation of CPSS was less than SF-36, the sample size calculation of SF-36 was selected. This would require 122 participants, inflated to about 150 to account for the loss to follow-up of approximately 20% of participants, with 75 participants being assigned to each group.

Participants

Inclusion criteria

1. Male or non-pregnant women aged from 18 to 80 years;
2. Patients who met the diagnosis criteria of chronic coronary syndrome included in[18];
3. NYHA class I, П;
4. Participants who understood the purpose of the clinical trial and voluntarily participate with signed informed consent.

Exclusion criteria

1. Acute myocardial infarction (AMI) within 2 weeks;
2. Severe aortic stenosis;
3. Hypertrophic cardiomyopathy;
4. Severe valvular heart disease;
5. Malignant tachyarrhythmia;
6. Poor patient compliance and incompletion of the clinical trial for not satisfying the requirements;
7. Patients with abnormal motor function caused by nervous system deterioration, motor system disease or rheumatic disease;
8. Those who regularly practice Tai Chi during the previous 3 months.

Setting and Recruitment

This multicenter study will be performed at the Beijing Normal University in China.

Recruitment and exercise training will occur at the Chinese PLA General Hospital, China, Beijing Shuili Hospital, China, and Anzhen Community Health Service Center, Beijing Chaoyang District, China. One hundred and fifty participants are to be recruited and the recruitment is scheduled to begin in October 2019. Combinations of advertising strategies include flyers within the hospital, advertisements in the print, online media, a major messaging platform (WeChat), clinics and databases.

Randomization, allocation concealment and blinding

After informed consent is signed, all patients will be randomized into either an intervention group receiving a 12-week TCCRP or a control group receiving CER. The random allocation sequence will be produced by an independent statistician via the PLAN sentences of the statistical software SAS 9.2 in a 1:1 ratio. Next, these assignments will be sent to a study staff member, exclusive to the study coordinator or principal investigator, who will store them into sealed, opaque envelopes with date and signature labels placed over the seals of the envelopes. The randomization envelopes will not be opened unless a participant meets eligibility criteria, completes the informed consent, and undergoes a baseline assessment. The study is conducted in 3 different cycles. Each cycle consists of a TCCRP group (intervention group) and CER group (control group). Each resulting group consists of 25 patients, equating to a 50 patients participating in each cycle, with a total of 150 patients over the course of the 3 cycles comprising the study. The instructors are randomly assigned to the 3 cycles.

Given the nature of the intervention, it is impossible to blind the patients or any personnel who are directly involved in conducting the programs. However, all outcome assessors, laboratory technicians, data managers and statisticians will be kept blind of the treatment allocations.

Patient and Public Involvement

We gave priority to patients as far as possible. Patients are the major factor to be consider when designing the trial, subject recruitment and data sharing. Since the very beginning of our study, we have constructed a Patient Public Involvement group.

During the group meeting, Patient Public Involvement group members were informed about how the study will be conducted. We always take a lot of time to communicate with patients about how to improve the detail of study to improve their compliance and they have given some good advice. For example, the patients suggested us to prepare simple booklet to introduce our study during the outpatients visit and by internet, also to enlarge the recruitment extent by WeChat and app of our hospital. We planned to disseminate our research to the participants and the public, such as publicizing our research in hospital official accounts and various academic lectures.

Interventions

Tai Chi cardiac rehabilitation program (TCCRP) group

Patients in the intervention group will receive TCCRP conducted by a cardiac rehabilitation team consisting of cardiologists, cardiology nurses, Tai Chi coaches and research assistants. Procedures and activities of the TCCRP include: (1) Tai Chi exercise, (2) evaluation of exercise ability, (3) education covering topics related to the exercise, and (4) a series of adherence strategies.

TCCRP pre-phase: a 2-week exercise before the start of exercise

1. TCCRP training

Six professional coaches with at least 10 years of Tai Chi teaching experience will be employed to teach and guide the participants' training. TCCRP will include (a) traditional Tai Chi warm-up exercises, followed by (b) Bafa Wubu of Tai Chi, (c)Tai Chi elastic belt exercise and (d) Tai Chi cool-down exercises.

(a) Tai Chi warm-up exercises (10 minutes) will include traditional breathing methods (full-body breathing), weight shifting, arm-swinging etc. These exercises will help release tension in the physical body, incorporate mindfulness and imagery into movement, increase breathing awareness and promote overall relaxation of the body and mind.

(b) The core Tai Chi movements (30 minutes) will be adapted from the Bafa Wubu of Tai Chi (also known as "eight methods and five footwork", Fig. 2), which include introductory routines to Tai Chi characterized with simple structures and rich

connotations performed repetitively. Technically speaking, the "Bafa" consists eight hand techniques, namely "Peng (warding off), Lu (rolling back), Ji (pressing), An (pushing), Cai (pulling down), Lie (splitting), Zhou (elbowing) and Kao (shouldering)"; while the "Wubu" consists five footwork, namely "Jin (advancement), Tui (retreat), Gu (shifting left), Pan (shifting right) and Ding (central equilibrium).

(c) Tai Chi combined with light-weight resistance band exercises(10 minutes) will include Tai Chi "Open and Close" movement, Tai Chi Spinning movement and Tai Chi Twining movement.

(d) Tai Chi cool-down exercises (10 minutes) will include various relaxation methods, such as regulating breath, regulating body and regulating mind.

Patients are required to practice the TCCRP until they master it. Mastery will be determined by the professional coaches. The mastery of Tai Chi was assessed and quantified due to the following 6 factors: the body shape should keep straight and upright; the gravity center shift is right; the action moves in an order; moving speed has a sense of rhythm; action and movement contains wring and screwing; every set consumes similar time. We have constructed a testing committee including 10 Tai Chi exports who had discussed together and summerized a scoring criteria concerning the above 6 dimensions. Six professional coaches with more than 10 years of Tai Chi teaching experiences were trained about the scoring system and then coached the subjects. At the end of learning stage, 3 of coaches were chosen randomly to work as the examiner. The professional coaches scored on a percentile basis according to the above 6 dimensions. Only the participants who gained an average score higher than 80 would be certificated to be qualified and move on the to the trial step.

2. Evaluation of exercise ability (week − 1 to week 0):

(a) Evaluation is conducted by cardiologists and physiotherapists;

(b) Evaluation is based on reviewing medical history, cardiopulmonary exercise test results and the performance of Tai Chi (heart rate and oxygen consumption will be recorded while performing Tai Chi);

(c) Evaluation results will guide the goal-setting process during consultation;

3. Education covering topics related to exercise:
   (a) Basic knowledge of chronic heart disease,
   (b) Basic knowledge of exercise-based cardiac rehabilitation.

TCCRP exercise phase: a 12-week intervention period

Participants will perform the TCCRP 3 times a week for 12 weeks. Each training session is 60 minutes and includes Tai Chi warm-up exercises (10 minutes), Bafa Wubu of Tai Chi (30 minutes), Tai Chi combined with light-weight resistance band exercises (10 minutes) and Tai Chi cool-down exercises (10 minutes). All participants will be encouraged to practice Tai Chi according to an instructional video until the end of the 12-week period.

Researchers will record the subjects' heart rate and blood pressure before and after training. During the training, the exercise intensity will be assessed by the Borg Rating of Perceived Exertion Scale (RPE Scale),[21] which is a frequently used quantitative measure of perceived exertion during exercise.

TCCRP follow-up phase: a 12-weeek follow-up period

After the 12-week TCCRP intervention, there will be a 12-week follow-up period that excludes any active rehabilitation. During the follow-up period, the participants will be asked to fill out forms to record the times and durations of their Tai Chi exercise or other physical activities and any incidence of a major adverse cardiac event. The forms will be returned to the researchers for follow-up each week by email or WeChat.

CER group (Control group)

Participants in the control group will receive a CER 3 times a week for 12 weeks. Each training session lasts for 60 minutes, including ordinary warm-up exercises (10 minutes), aerobic activity (30 minutes), resistive exercise (10 minutes) and cool-down exercises (10 minutes). Each training session includes: (1) an active warm-up including

arm-swinging, gentle stretches of the neck, shoulders, spine, arms and legs; (2) an aerobic activity comprising primarily cycle ergometer exercise; (3) resistive exercise mainly including resistance band exercises; and (4) a cool-down session involving active and static stretching exercises with primary body movements.

The CER program is consistent with the current recommended guidelines of moderate intensity exercises (50 to 80% Heart Rate Reserve (HRR): Rated Perceived Exertion 11–13) for CHD patients**.** Our program is individually tailored to each participant alongside close supervision. The program will be introduced and increased in duration and intensity gradually to achieve the target of moderate-intensity exercise.

Concomitant treatment

Participants in both groups will continue routine medications, such as aspirin, metoprolol, anti-platelet and anti-coagulant drugs or beta-adrenergic blockers, according to patients' respective conditions and will maintain their usual treatment visits throughout the study. All procedures and medication prescriptions will be determined by physicians following the clinical guidelines.[22 23] The specific date and reasons of any medical therapy changes will be recorded in the case report form (CRF).

Outcome measures

All outcome measures will be collected by 3 research assistants at 2 weeks (baseline), 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up). Demographic information collected will include age, gender, ethnicity, marital status, education level, accommodation type and postal address. Clinical information will also be obtained from the patients' clinical records by a member of their hospital research team. All data collected from the assistants and therapists will be stored in a dedicated computer for the study and will be kept in a secure and lock-protected location.

Primary outcome measures

1. The SF-36 Health Survey (SF-36) is a multi-purpose, short-form health survey with only 36 questions.[24] SF-36 items cover eight domains: physical functioning, role limitations due to physical health problems, body pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. Higher scores indicate higher levels of health. SF-36 will be evaluated at baseline, 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up).
2. Chinese Perceived Stress Scale (CPSS) is a self-rated questionnaire that assesses perceived stress.[25]CPSS consists 14 items that are divided into two categories: sense of tension and loss of control. Higher scores indicate higher levels of stress. CPSS will be evaluated at baseline, 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up).

Secondary outcome measures

1. Body composition measurements will include fat mass, body fat (percentage), fat-free mass and lean body mass. These measurements will be taken by bioelectrical impedance analysis using an Inbody 770 (Biospace Co) at baseline, 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up).
2. Cardiopulmonary exercise test (CPET) is an objective method being increasingly used in a wide spectrum of clinical practice for assessing the functional capacity of CHD patients. Indexes include changes in VO_2 peak and VAT and VE/ VCO_2 slope in the cardiopulmonary exercise test (CPET) at the end of the 3-month intervention.
3. Respiratory muscle function will be measured by POWER breath K-5. Indexes include changes in S-Index, Peak PIF of inspiratory velocity and power at the end of the 3-month intervention.
4. Locomotor skills includes handgrip strength, balance and flexibility. Handgrip strength, which is used to determine the maximum isometric strength of the hand and forearm muscles, will be measured using the handgrip strength dynamometer produced by CAMRY (product type EH101). The best result from repeated tests

of each hand will be recorded. The balance will be evaluated by using the time duration until losing balance. We respectively investigated the time duration of standing on one foot with eyes closed, standing on one foot with eyes open, strengthening Romberg's test[26]. The participants were tested three times to record their time until they lost their balance. Finally, the best of the three was selected. Time difference were calculated as the time duration after treatment minus that before treatment. Flexibility will be measured by seated forward flexion test. Locomotor skills will be evaluated at baseline and at the end of the 3-month intervention.

5. An echocardiogram comprising LVED Vi and LVEF using echocardiography will be assessed at baseline and at the end of the 3-month intervention. NYHA classification will also be evaluated at baseline and at the end of the 3-month intervention.
6. Heart rate recovery time will be measured. Heart rate recovery time will record heart rate 1 to 6 minutes after Tai Chi exercise, power cycling and resistance exercise.
7. A laboratory examination will be performed that includes glycolipid metabolism, inflammatory factor level, immunologic function and oxidative stress index. The laboratory examination will be evaluated at baseline and at the end of the 3-month intervention.
8. The Berg Balance Scale (BBS) is a widely used clinical test of a person's static and dynamic balance abilities[27], and comprises of a set of 14 simple balance related tasks, ranging from standing up from a sitting position to standing on one foot. Total score ranges from 0 to 56, with 0 to 20 corresponding to a high fall risk, 21 to 40 a medium fall risk and 41 to 56 a low fall risk. The Berg Balance Scale will be evaluated at baseline and at the end of the 3-month intervention.
9. The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire that assesses sleep quality and disturbances.[28] It contains 19 self-answered questions for the subject and 5 peer-answered questions for the bed partner or a roommate (if

one is available). The scores from seven categories are added to calculate the index, ranging from 0 to 21. A score of zero indicates no disturbance in sleep or good sleep quality, whereas higher scores indicate poorer sleep quality. The PSQI will be evaluated at baseline and at the end of the 3-month intervention.

10. Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7(GAD-7) are validated self-answered questionnaires that assess levels of depression and anxiety. Higher scores reflect greater levels of anxiety and depression. PHQ-9 and GAD-7 will be evaluated at baseline and at the end of the 3-month intervention.
11. The Seattle Angina Score (SAQ) will be used to determine the total number of 9 problems and the 5 aspects of CAD, including the degree of physical activity, the stability and frequency of angina, the degree of satisfaction of the treatment, and the perception of the disease. The higher the score, the better the quality of life and body function. SAQ will be measured at baseline and at the end of the 3-month intervention.
12. A record will be made of any side effects and possible adverse reactions arising from the intervention.

Safety measurements

All study participants are monitored weekly during the study intervention for the occurrence of adverse events defined by any undesirable experience. All adverse events that occur during the study will be recorded on the Adverse Event Case Report Form and will be evaluated for relevance to the intervention. All adverse events will also be reported to the Human Research Committee promptly in accordance with guidelines.

Only patients who are eligible and capable of completing the test will undergo a Cardiopulmonary Exercise Test (CPET). For enrolled patients meeting the rehabilitation training standards, they will be stratified according to the degree of motion risk and appropriate exercise intensity and time will be adjusted based on their risk stratification. Before the cardiac rehabilitation exercise, researchers will educate

patients about the CHD rehabilitation exercises, including training contraindications and exercise advisories regarding the respective CER and TCCRP exercises. Moreover, the cardiac rehabilitation Center of Chinese PLA General Hospital, Beijing Shuili Hospital and Anzhen Community Health Service Center are equipped with a comprehensive set of rescue equipment. A thorough contingency plan and rescue procedure for cardiovascular events has also been formulated prior to the commencement of the research. Should an adverse event occur during the exercise, the researchers will immediately initiate the contingency plan to circumvent the occurrence of any fatal outcomes.

Data management and monitoring

Beijing Normal University will be responsible for monitoring research progress, managing the data and performing statistical analyses. The research assistants will be responsible for checking the integrity of the completed CRF and for timely entry of the collected data into the EpiData Manager, a free data management software. The project manager will be responsible for initial data cleaning, identifying, coding and converting the data into the proper format for analysis. All investigators involved in data management and analysis will be blinded to treatment allocation.

Statistical analysis

Continuous variables will be described as mean ± standard deviation (SD) for normal distributions or median for non-normal distributions, categorical variables will be described as frequency. Baseline data mainly describe the clinical characteristic and features of the subjects. We also tested the equalization of the two groups of variables. Continuous variables will be described as a two-sample Student's t-test for normal distributions or Wilcoxon test for non-normal distributions. Categorical variables will be described as the chi-square test. The group difference between intervention and control group at each time point (4 and 12 weeks after intervention or 12-week follow-up period) will be analysed using Student's t-test or Mann-Whitney U-test. A two-way

analysis of variance with repeated measures will be used to determine the effects of time and group on our dependent variables. A Bonferroni-adjusted post hoc analysis will be conducted when time-group interaction was detected. The analysis of primary or secondary outcomes will be based on an intention to treat (ITT) principle, and participants who either drop out from the study or fail to adhere to the protocol will have their last known data carried forward. The missing data will be imputed using a multiple imputation method. All data will be analyzed with SPSS 21.0 (IBM, Chicago, IL, USA) software packages. Statistical significance is defined as a two-sided *P* value < 0.05.

Adherence

During the 3-month treatment period, participants will be asked to practice strictly according to the training program and will not be allowed to take part in any new or additional exercise programs. Throughout the 3-month intervention period, the researchers will track the number of missed sessions for each participant during the intervention period. Participants' attendance will be monitored during each in-person session by staff-completed attendance forms and class sign-in sheets. The percentage of compliance will be documented on the case report form. The rate of patient compliance = (total planned number of times − number of absence) / total number of times × 100%. A compliance rate of 80% or greater will be considered as good, whereas a compliance rate of less than 80% is considered as poor. An attendance of less than 20% will be considered as a dropout from the study.

DISCUSSION

The development of an ideal and effective cardiac rehabilitation program is still being explored and current cardiac rehabilitation mainly consists of contemporary conventional exercises. In fact, current cardiac rehabilitation programs have been reported to be underdeveloped and limited, reflected by a poor level of involvement with less than 30% of patients participating in the existing offerings.[29] As such, there is

an unmet need for reforms and the provision of alternative cardiac rehabilitation programs to encourage the growth of cardiac rehabilitation. The exploration of an ideal cardiac rehabilitation exercise that is most beneficial for CCS patients should be determined.

This trial is the first one to compare the safety, feasibility and benefits of TCCRP and CER in CCS patients. There are several strengths of our trial: Firstly, the proposed research study is unique and the first study about a Bafa Wubu of Tai Chi which is a new Tai Chi school. Secondly, TCCRP in this study was specifically designed for patients with CCS. Finally, this is the first time for Tai Chi study to develop a comparative training system to match the conventional exercise. Our study will supply scientific evidence for the promotion of Bafa Wubu of Tai Chi at home and abroad.

TCCRP has some features which make it more suitable for CCS patients. Firstly, the intensity of TCCRP is low, and it is much safer for patients with CCS. Secondly, TCCRP is much easier to be learned and possesses a simple structure of movements, a reasonable number of postures, and fewer practice environment limitations. Thirdly, TCCRP is not limited by location and easy to be carried out. Finally, TCCRP doesn't need money or any equipment. To sum up, compared with conventional exercise rehabilitation (CER), TCCRP is more suitable for CCS patients.

Compared with conventional exercise styles (e.g. aerobic, resistance, and extensibility exercise), Tai Chi typically involves a mind–body integration practice that combines the coordination of slow movements with mental focus, deep breathing, and relaxation for promoting both physical and mental well-being.[30-32] Previous studies have shown that regular Tai Chi exercise is beneficial in improving psychological and physiological outcomes among the elderly and various clinical populations (e.g. Parkinson's disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD) and psychological illness).[33-36] As a typical mind–body exercise which incorporates the characteristics of Traditional Chinese Medicine, Tai Chi may be considered to be an effective exercise to promote health in a diverse range of populations (e.g. healthy population, patients with chronic diseases, youths, middle-

aged or elderly adults) .[37 38]

Compared with other Tai Chi schools, TCCRP has distinct advantages for CCS patients. TCCRP utilized Bafa Wubu of Tai Chi, namely, introductory routines to Tai Chi characterized by simple structures. Of the many styles of Tai Chi, however, it is hard to further popularize and generalize, due to its numerous movements and complexity, especially among patients with CCS. By upholding scientific, standardized and simplified principles, the Bafa Wubu of Tai Chi is systematically refined and sorted out on the basis of the other forms of Tai Chi, and the two exercise forms of "standing" and "marching", thus forming a set of Tai Chi routines for popularization characterized by culture, fitness and simplicity. Compared with the others, Bafa Wubu of Tai Chi is safer and much easier to be mastered for patients with CCS.

It should be acknowledged that this study has several limitations. It is difficult to monitor any additional physical activity of participants during the study duration. Although all participants will be required to record their daily physical activity or exercise information with a pedometer, this is not sufficiently accurate to track their daily activity intensity. Furthermore, due to the nature of the exercise interventions (Tai Chi versus CER), the blinding of participants is unachievable in this trial. However, every effort will be made to ensure that the outcome assessors, data managers and statisticians participating in this study will be kept blind of the treatment allocations.

In conclusion, this study aims to assess the efficacy, safety and acceptability of an innovative TCCRP for CCS patients. The finding will be vital to help establish an optimal cardiac rehabilitation program for treating CCS patients.

TRIAL STATUS

This trial is currently in the recruitment phase. Estimated completion of the trial is expected to be completed by December 2020.

Additional files

Abbreviations

CHD: coronary heart disease; CCS: chronic coronary syndrome; ACS: acute coronary syndromes; TCCRP: Tai Chi cardiac rehabilitation program; TCM: Traditional Chinese Medicine; CER: conventional exercise rehabilitation.

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Authors' contributions

LSJ, MJ, and YHC conceived and designed the study protocol. The individual interviews were conducted by MJ, LH, ZLS, and GAY. ZJW and MJ performed the translation and analysed the data. ZJW, YW, CZH, WQY, CMZ, LYM, LYL, GTM, LCH, SB and WHW guided and supervised the Tai Chi training. MJ and ZJW contributed to writing and reading the manuscript. All authors approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

The data capture system and web servers will be provided by the data management center of Beijing Normal University (http://cas.bnu.edu.cn/cas/login) and the data management belongs to the Wushu and National Traditional Sports Culture Promotion Research Center of Beijing Normal University. The results of the review will be disseminated through peer-reviewed publications.

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Table 1: Schedule for data collection; outcome measures per visits

Items	Phase I: Screening	Phase II: Baseline	Phase III: Month 1	Phase IV: Month 3	Phase V: Month 6
Inclusion/exclusion criteria	√				
Diagnostic index	√				
Signed informed consent	√				
Randomization and allocation	√				
Safety index	√	√	√	√	
General clinical information		√		√	
Primary outcomes		√		√	
Secondary outcomes		√		√	
Other indicators		√		√	
Recurrent cardiovascular events			√	√	√
Adherence			√	√	√
Adverse events			√	√	
Summary at the end of the study					√

Figure legend

Figure 1: Flow diagram of study design

SF-36 means the SF-36 Health Survey; CPSS means Chinese Perceived Stress Scale; NYHA means New York Heart Association; SAQ means Seattle Angina Scale; PSQI means Pittsburgh Sleep Quality Index; PHQ-9 means Patient Health Questionnaire-9; GAD-7 means Generalized Anxiety Disorder-7; BBS means Berg Balance Scale.

Figure. 2: Exemplary Bafa Wubu of Tai Chi; the pictures have taken the portrait right; the fugleman is the developer of TCCRP.

The “Bafa” consisted of eight hand techniques were shown in figure 2. Each figure showed each hand technique, namely “Peng (warding off), Lu (rolling back), Ji (pressing), An (pushing), Cai (pulling down), Lie (splitting), Zhou (elbowing) and Kao (shouldering)”.

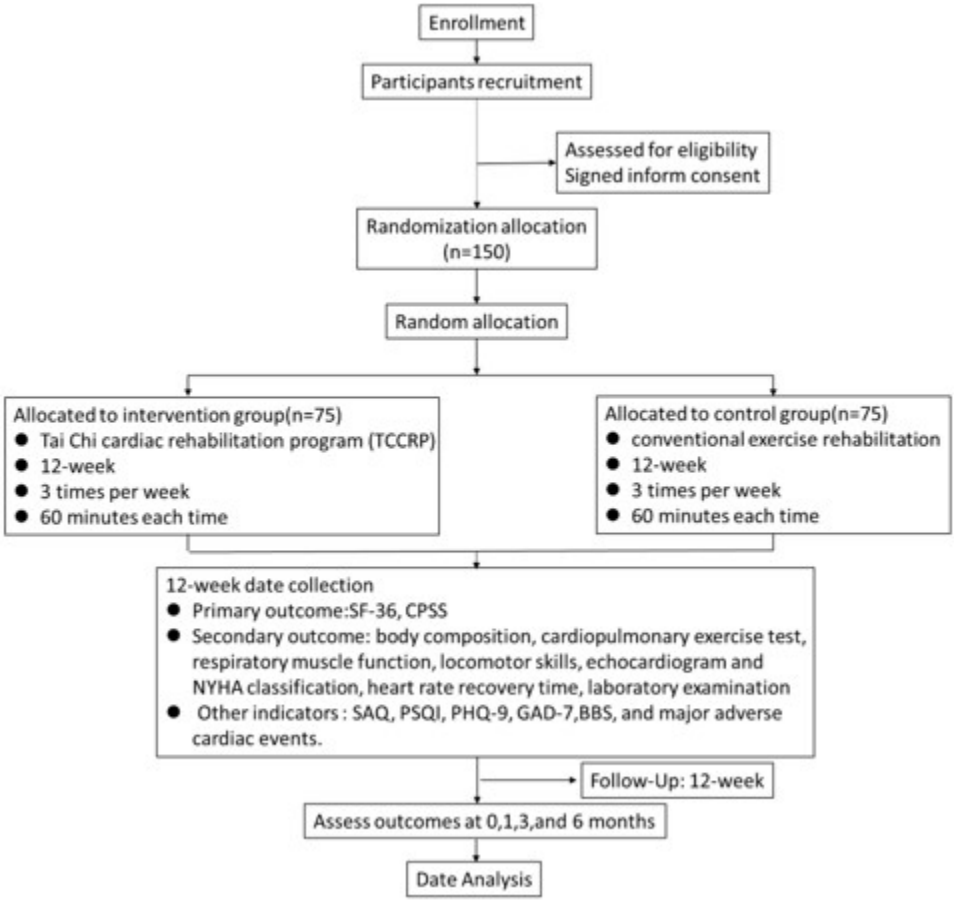

Figure 1: Flow diagram of study design

126x119mm (96 x 96 DPI)

Figure. 2: Exemplary Bafa Wubu of Tai Chi; the pictures have taken the portrait right; the fugleman is the developer of TCCRP.

149x99mm (96 x 96 DPI)

BMJ Open

Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Chronic Coronary Syndrom Patients: Study Protocol for a Randomized Controlled Trial

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Primary Subject Heading:	Sports and exercise medicine
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Keywords:	Coronary heart disease < CARDIOLOGY, SPORTS MEDICINE, COMPLEMENTARY MEDICINE, EDUCATION & TRAINING (see Medical Education & Training), REHABILITATION MEDICINE, Clinical trials < THERAPEUTICS

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Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Chronic Coronary Syndrom Patients: Study Protocol for a Randomized Controlled Trial

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Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Chronic Coronary Syndrom Patients: Study Protocol for a Randomized Controlled Trial

ABSTRACT

Introduction: Preliminary evidence from clinical observations suggests that Tai Chi exercise may offer potential benefits for patients with chronic coronary syndrom(CCS). However, the advantages for CCS patients to practice Tai Chi exercise as rehabilitation have not been rigorously tested and there is a lack of consensus on its benefits. This study aims to develop an innovative Tai Chi Cardiac Rehabilitation Program (TCCRP) for CCS patients and to assess the efficacy, safety and acceptability of the program.

Methods and analysis: We propose to conduct a multicenter randomized-controlled clinical trial comprising of 150 participants with CCS. The patients will be randomly assigned in a 1:1 ratio into two groups. The intervention group will participate in a supervised TCCRP held 3 times a week for 3 months. The control group will receive supervised conventional exercise rehabilitation (CER) held 3 times a week for 3 months. The primary and secondary outcomes will be assessed at baseline, 1 month, 3 months after intervention and after an additional 3 months follow-up period. Primary outcome measures will include a score of 36-Item Short Form Survey and Chinese Perceived Stress Scale. The secondary outcome measures will include body composition, cardiopulmonary exercise test, respiratory muscle function, locomotor skills, echocardiogram, New York Heart Association classification, heart rate recovery time and laboratory examination. Other measures also include Seattle Angina Scale, Pittsburgh Sleep Quality Index, Patient Health Questionnaire-9, Generalized Anxiety Disorder-7 and Berg Balance Scale. All adverse events will be recorded and analyzed.

Ethics and dissemination: This study conforms to the principles of the Declaration of Helsinki and relevant ethical guidelines. Ethical approval has been obtained from the Ethics Committee of Chinese PLA General Hospital (approval number: S2019-060-02). Findings from this study will be published and presented at conferences for widespread dissemination of the results.

Trial registration number: ClinicalTrials.gov identifier: NCT03936504

Strengths and limitations of this study:

- The proposed research study is unique and the first study about a Bafa Wubu of Tai Chi which is a new Tai Chi school.
- TCCRP in this study was specifically designed for patients with CCS.
- This is the first time for Tai Chi study to develop a comparative training system to match the conventional exercise.
- It is difficult to exclude the effect of other physical activity due to difficulty of monitoring.
- The blinding of participants is unachievable in this trial; however, efforts will be made to ensure that the data is blinded.

Keywords: Tai Chi, Coronary heart disease, Chronic coronary syndrom, Safety, Effectiveness, Randomized controlled trial, Exercise rehabilitation.

INTRODUCTION

Coronary heart disease (CHD) remains the major cause of morbidity and mortality worldwide. CHD responsible for about one in every seven deaths; and, China Heart Society is predicted to continue until 2030, accounting for 14% of all deaths globally.[1] [2] Despite the use of effective Western medicine treatments, the incidence of CHD continues to rise and is associated with a high mortality rate. Cardiac rehabilitation (CR), especially exercise training is proven to significantly alleviate the cardiac symptoms, preserve the heart function, and improve the clinical outcomes. Therefore cardiac rehabilitation is recommended by many guidelines of different countries.[3-9] However, latest study demonstrated only 24.4% CR-eligible Medicare beneficiaries participated in CR and marked disparities were observed.[10] Besides limitation of medical resource, poor compliance of patients remains main reason. An effective and attractive CR training system is urgently needed.

These years the integration of Traditional Chinese medicine (TCM) with Western

medicine to treat CHD has made great progress. As an effective complementary therapy, TCM has been demonstrated to improve the prognosis of CHD patients.[11] Tai Chi is an important element of TCM which combines the meridians and collateral theory, Yin-Yang theory and Five-element theory. Tai Chi exercise contains three core elements, namely "body", "breath" and "mind", as pronounced in Chinese as "Xing", "Qi", "Yi" respectively. The spirits of Tai Chi are summarized to "building the body", "conveying the breath" and "using the mind". Previous studies have shown that regular Tai Chi exercise was beneficial in improving psychological and physiological outcomes among CHD patients.[12-15] Study by Professor Salmorirago-Blocthcer have showed patients receiving Tai Chi exercise exhibited much better compliance than those receiving conventional exercise. [12]

There are many schools in Tai Chi such as the Yang-style, Wu-style, Chen-style, Wu-style and Sun-style, wherein each style takes a different approach in terms of the movements and forms. Furthermore, as Tai Chi exercise comprises many assorted movements that can be also complex to perform, it is difficult to popularize and simplify the exercise, especially in elderly patients and patients with chronic diseases.

Based on prior insights of the Tai Chi movements obtained from our studies and other work,[16] [17] our research team developed an innovative Tai Chi Cardiac Rehabilitation Program (TCCRP) specifically for CHD patients. However, as the value of TCCRP has not yet to be clinically proven, a clinical trial is required to validate the benefits of adopting this exercise for CHD patients.

CHD can be categorized as either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) due to pathophysiological features and clinical prognosis because it is dynamic process of atherosclerotic plaque accumulation and functional alterations of coronary circulation[18]. Between the two process, most CHD patients stay in the CCS state. Latest studies revealed patients with CCS benefit a lot from cardiac rehabilitation programs characterized by life style therapy[18]. So we chose CCS patients as our subjects. This study aims to assess the efficacy, safety, and acceptability of TCCRP for CCS patients.

The primary hypothesis is that TCCRP (the intervention group) will improve the life quality and reduce the stress when compared against conventional exercise rehabilitation (CER, the control group). Secondary objectives are to evaluate the effects of the TCCRP on body composition, cardiopulmonary exercise test, respiratory muscle function, locomotor skills, echocardiogram, New York Heart Association (NYHA) classification, heart rate recovery time and laboratory examination. Other indicators measured will include Seattle Angina Scale (SAQ), Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), Berg Balance Scale (BBS) and major adverse cardiac events. Additional objectives to be explored will include: (1) the influence of potential factors on the adherence to the TCCRP; (2) the safety of the TCCRP and (3) individual experiences and acceptability following the TCCRP.

METHODS/DESIGN

Study design

This is a prospective, multicenter, randomized-controlled clinical trial comparing a TCCRP with CER with an allocation ratio of 1:1. The study period lasts for 6 months including a 3-month supervised intervention and a 3-month follow-up with the primary outcomes measured at baseline, 1 month, 3 months and 6 months. Secondary outcomes will be measured at baseline and after a 3-month intervention period. A brief flowchart of the entire study is shown in Figure 1 and the schedule of events is provided in Table 1. The study protocol is reported according to Standard Protocol Items: Recommendations for Intervention Trials 2013 (SPIRIT). A SPIRIT Checklist is provided in the online supplementary additional file1. The study protocol was submitted to the Ethics Committee of Chinese PLA General Hospital on 26 January 2019. After 2 revisions, and final version 3 of the protocol was approved on 2 June 2019(approval number: S2019-060-02). This study is registered on ClinicalTrial.gov (NCT03936504).

Sample size calculation

Sample size calculation will be based on the co-primary outcomes of the RCT. The SF-36 Health Survey (SF-36) and Chinese Perceived Stress Scale (CPSS) are being set as the co-primary outcome and used for sample size calculation. Sample size was calculated on the basis of the changes in the SF-36 and CPSS between comparison groups with a significance level of 5% and a two-tailed critical region to ensure the same effect size with 80% power by G*power V.3.1.9.4 software. The means and their SDs (mean ±SD) of the SF-36 and CPSS in the control and intervention group were (64.30±13.11, 71.79±16.03)[19] and (42.31±8.17, 35.15±6.82)[20], respectively, at postintervention according to the published literature. Because the sample size calculation of CPSS was less than SF-36, the sample size calculation of SF-36 was selected. This would require 122 participants, inflated to about 150 to account for the loss to follow-up of approximately 20% of participants, with 75 participants being assigned to each group.

Participants

Inclusion criteria

1. Male or non-pregnant women aged from 18 to 80 years;
2. Patients who met the diagnosis criteria of chronic coronary syndrome included in[18];
3. NYHA class I, Π;
4. Participants who understood the purpose of the clinical trial and voluntarily participate with signed informed consent.

Exclusion criteria

1. Acute myocardial infarction (AMI) within 2 weeks;
2. Severe aortic stenosis;
3. Hypertrophic cardiomyopathy;
4. Severe valvular heart disease;

5. Malignant tachyarrhythmia;
6. Poor patient compliance and incompletion of the clinical trial for not satisfying the requirements;
7. Patients with abnormal motor function caused by nervous system deterioration, motor system disease or rheumatic disease;
8. Those who regularly practice Tai Chi during the previous 3 months.

Setting and Recruitment

This multicenter study will be performed at the Beijing Normal University in China. Recruitment and exercise training will occur at the Chinese PLA General Hospital, China, Beijing Shuili Hospital, China, and Anzhen Community Health Service Center, Beijing Chaoyang District, China. One hundred and fifty participants are to be recruited and the recruitment is scheduled to begin in October 2019. Combinations of advertising strategies include flyers within the hospital, advertisements in the print, online media, a major messaging platform (WeChat), clinics and databases.

Randomization, allocation concealment and blinding

After informed consent is signed, all patients will be randomized into either an intervention group receiving a 12-week TCCRP or a control group receiving CER. The random allocation sequence will be produced by an independent statistician via the PLAN sentences of the statistical software SAS 9.2 in a 1:1 ratio. Next, these assignments will be sent to a study staff member, exclusive to the study coordinator or principal investigator, who will store them into sealed, opaque envelopes with date and signature labels placed over the seals of the envelopes. The randomization envelopes will not be opened unless a participant meets eligibility criteria, completes the informed consent, and undergoes a baseline assessment. Informed consent will be obtained by two blinded research assistants prior to the baseline assessment. Eligible participants will receive the information about this trial and have an informed discussion with two trained research assistants regarding the information provided.

The study is conducted in 3 different cycles. Each cycle consists of a TCCRP group (intervention group) and CER group (control group). Each resulting group consists of 25 patients, equating to a 50 patients participating in each cycle, with a total of 150 patients over the course of the 3 cycles comprising the study. The instructors are randomly assigned to the 3 cycles.

Given the nature of the intervention, it is impossible to blind the patients or any personnel who are directly involved in conducting the programs. However, all outcome assessors, laboratory technicians, data managers and statisticians will be kept blind of the treatment allocations.

Patient and Public Involvement

We gave priority to patients as far as possible. Patients are the major factor to be consider when designing the trial, subject recruitment and data sharing. Since the very beginning of our study, we have constructed a Patient Public Involvement group. During the group meeting, Patient Public Involvement group members were informed about how the study will be conducted. We always take a lot of time to communicate with patients about how to improve the detail of study to improve their compliance and they have given some good advice. For example, the patients suggested us to prepare simple booklet to introduce our study during the outpatients visit and by internet, also to enlarge the recruitment extent by WeChat and app of our hospital. We planned to disseminate our research to the participants and the public, such as publicizing our research in hospital official accounts and various academic lectures.

Interventions

Tai Chi cardiac rehabilitation program (TCCRP) group

Patients in the intervention group will receive TCCRP conducted by a cardiac rehabilitation team consisting of cardiologists, cardiology nurses, Tai Chi coaches and research assistants. Procedures and activities of the TCCRP include: (1) Tai Chi exercise, (2) evaluation of exercise ability, (3) education covering topics related to the exercise, and (4) a series of adherence strategies.

TCCRP pre-phase: a 2-week exercise before the start of exercise

1. TCCRP training

Six professional coaches with at least 10 years of Tai Chi teaching experience will be employed to teach and guide the participants' training. TCCRP will include (a) traditional Tai Chi warm-up exercises, followed by (b) Bafa Wubu of Tai Chi, (c)Tai Chi elastic belt exercise and (d) Tai Chi cool-down exercises.

(a) Tai Chi warm-up exercises (10 minutes) will include traditional breathing methods (full-body breathing), weight shifting, arm-swinging etc. These exercises will help release tension in the physical body, incorporate mindfulness and imagery into movement, increase breathing awareness and promote overall relaxation of the body and mind.

(b) The core Tai Chi movements (30 minutes) will be adapted from the Bafa Wubu of Tai Chi (also known as "eight methods and five footwork", Fig. 2), which include introductory routines to Tai Chi characterized with simple structures and rich connotations performed repetitively. Technically speaking, the "Bafa" consists eight hand techniques, namely "Peng (warding off), Lu (rolling back), Ji (pressing), An (pushing), Cai (pulling down), Lie (splitting), Zhou (elbowing) and Kao (shouldering)"; while the "Wubu" consists five footwork, namely "Jin (advancement), Tui (retreat), Gu (shifting left), Pan (shifting right) and Ding (central equilibrium).

(c) Tai Chi combined with light-weight resistance band exercises(10 minutes) will include Tai Chi "Open and Close" movement, Tai Chi Spinning movement and Tai Chi Twining movement.

(d) Tai Chi cool-down exercises (10 minutes) will include various relaxation methods, such as regulating breath, regulating body and regulating mind.

Patients are required to practice the TCCRP until they master it. Mastery will be determined by the professional coaches. The mastery of Tai Chi was assessed and quantified due to the following 6 factors: the body shape should keep straight and upright; the gravity center shift is right; the action moves in an order; moving speed has a sense of rhythm; action and movement contains wring and screwing; every set

consumes similar time. We have constructed a testing committee including 10 Tai Chi experts who had discussed together and summerized a scoring criteria concerning the above 6 dimensions. Six professional coaches with more than 10 years of Tai Chi teaching experiences were trained about the scoring system and then coached the subjects. At the end of learning stage, 3 of coaches were chosen randomly to work as the examiner. The professional coaches scored on a percentile basis according to the above 6 dimensions. Only the participants who gained an average score higher than 80 would be certificated to be qualified and move on the to the trial step.

2. Evaluation of exercise ability (week − 1 to week 0):

   (a) Evaluation is conducted by cardiologists and physiotherapists;

   (b) Evaluation is based on reviewing medical history, cardiopulmonary exercise test results and the performance of Tai Chi (heart rate and oxygen consumption will be recorded while performing Tai Chi);

   (c) Evaluation results will guide the goal-setting process during consultation;

3. Education covering topics related to exercise:

   (a) Basic knowledge of chronic heart disease,

   (b) Basic knowledge of exercise-based cardiac rehabilitation.

TCCRP exercise phase: a 12-week intervention period

Participants will perform the TCCRP 3 times a week for 12 weeks. Each training session is 60 minutes and includes Tai Chi warm-up exercises (10 minutes), Bafa Wubu of Tai Chi (30 minutes), Tai Chi combined with light-weight resistance band exercises (10 minutes) and Tai Chi cool-down exercises (10 minutes). All participants will be encouraged to practice Tai Chi according to an instructional video until the end of the 12-week period.

Researchers will record the subjects' heart rate and blood pressure before and after training. During the training, the exercise intensity will be assessed by the Borg Rating of Perceived Exertion Scale (RPE Scale),[21] which is a frequently used

quantitative measure of perceived exertion during exercise.

TCCRP follow-up phase: a 12-weeek follow-up period

After the 12-week TCCRP intervention, there will be a 12-week follow-up period that excludes any active rehabilitation. During the follow-up period, the participants will be asked to fill out forms to record the times and durations of their Tai Chi exercise or other physical activities and any incidence of a major adverse cardiac event. The forms will be returned to the researchers for follow-up each week by email or WeChat.

CER group (Control group)

Participants in the control group will receive a CER 3 times a week for 12 weeks. Each training session lasts for 60 minutes, including ordinary warm-up exercises (10 minutes), aerobic activity (30 minutes), resistive exercise (10 minutes) and cool-down exercises (10 minutes). Each training session includes: (1) an active warm-up including arm-swinging, gentle stretches of the neck, shoulders, spine, arms and legs; (2) an aerobic activity comprising primarily cycle ergometer exercise; (3) resistive exercise mainly including resistance band exercises; and (4) a cool-down session involving active and static stretching exercises with primary body movements.

The CER program is consistent with the current recommended guidelines of moderate intensity exercises (50 to 80% Heart Rate Reserve (HRR); Rated Perceived Exertion 11–13) for CHD patients**.** Our program is individually tailored to each participant alongside close supervision. The program will be introduced and increased in duration and intensity gradually to achieve the target of moderate-intensity exercise.

Concomitant treatment

Participants in both groups will continue routine medications, such as aspirin, metoprolol, anti-platelet and anti-coagulant drugs or beta-adrenergic blockers,

according to patients' respective conditions and will maintain their usual treatment visits throughout the study. All procedures and medication prescriptions will be determined by physicians following the clinical guidelines.[22 23] The specific date and reasons of any medical therapy changes will be recorded in the case report form (CRF).

Outcome measures

All outcome measures will be collected by 3 research assistants at 2 weeks (baseline), 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up). Demographic information collected will include age, gender, ethnicity, marital status, education level, accommodation type and postal address. Clinical information will also be obtained from the patients' clinical records by a member of their hospital research team. All data collected from the assistants and therapists will be stored in a dedicated computer for the study and will be kept in a secure and lock-protected location.

Primary outcome measures

1. The SF-36 Health Survey (SF-36) is a multi-purpose, short-form health survey with only 36 questions.[24] SF-36 items cover eight domains: physical functioning, role limitations due to physical health problems, body pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. Higher scores indicate higher levels of health. SF-36 will be evaluated at baseline, 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up).
2. Chinese Perceived Stress Scale (CPSS) is a self-rated questionnaire that assesses perceived stress.[25]CPSS consists 14 items that are divided into two categories: sense of tension and loss of control. Higher scores indicate higher levels of stress. CPSS will be evaluated at baseline, 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up).

Secondary outcome measures

1. Body composition measurements will include fat mass, body fat (percentage), fat-free mass and lean body mass. These measurements will be taken by bioelectrical impedance analysis using an Inbody 770 (Biospace Co) at baseline, 1 month, 3 months (at the end of intervention) and 6 months (at the 3-month follow-up).
2. Cardiopulmonary exercise test (CPET) is an objective method being increasingly used in a wide spectrum of clinical practice for assessing the functional capacity of CHD patients. Indexes include changes in VO_2 peak and VAT and VE/ VCO_2 slope in the cardiopulmonary exercise test (CPET) at the end of the 3-month intervention.
3. Respiratory muscle function will be measured by POWER breath K-5. Indexes include changes in S-Index, Peak PIF of inspiratory velocity and power at the end of the 3-month intervention.
4. Locomotor skills includes handgrip strength, balance and flexibility. Handgrip strength, which is used to determine the maximum isometric strength of the hand and forearm muscles, will be measured using the handgrip strength dynamometer produced by CAMRY (product type EH101). The best result from repeated tests of each hand will be recorded. The balance will be evaluated by using the time duration until losing balance. We respectively investigated the time duration of standing on one foot with eyes closed, standing on one foot with eyes open, strengthening Romberg ' s test[26]. The participants were tested three times to record their time until they lost their balance. Finally, the best of the three was selected. Time difference were calculated as the time duration after treatment minus that before treatment. Flexibility will be measured by seated forward flexion test. Locomotor skills will be evaluated at baseline and at the end of the 3-month intervention.
5. An echocardiogram comprising LVED Vi and LVEF using echocardiography

will be assessed at baseline and at the end of the 3-month intervention. NYHA classification will also be evaluated at baseline and at the end of the 3-month intervention.

6. Heart rate recovery time will be measured. Heart rate recovery time will record heart rate 1 to 6 minutes after Tai Chi exercise, power cycling and resistance exercise.
7. A laboratory examination will be performed that includes glycolipid metabolism, inflammatory factor level, immunologic function and oxidative stress index. The laboratory examination will be evaluated at baseline and at the end of the 3-month intervention.
8. The Berg Balance Scale (BBS) is a widely used clinical test of a person's static and dynamic balance abilities[27], and comprises of a set of 14 simple balance related tasks, ranging from standing up from a sitting position to standing on one foot. Total score ranges from 0 to 56, with 0 to 20 corresponding to a high fall risk, 21 to 40 a medium fall risk and 41 to 56 a low fall risk. The Berg Balance Scale will be evaluated at baseline and at the end of the 3-month intervention.
9. The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire that assesses sleep quality and disturbances.[28] It contains 19 self-answered questions for the subject and 5 peer-answered questions for the bed partner or a roommate (if one is available). The scores from seven categories are added to calculate the index, ranging from 0 to 21. A score of zero indicates no disturbance in sleep or good sleep quality, whereas higher scores indicate poorer sleep quality. The PSQI will be evaluated at baseline and at the end of the 3-month intervention.
10. Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7(GAD-7) are validated self-answered questionnaires that assess levels of depression and anxiety. Higher scores reflect greater levels of anxiety and depression. PHQ-9 and GAD-7 will be evaluated at baseline and at the end of the 3-month intervention.
11. The Seattle Angina Score (SAQ) will be used to determine the total number of 9

problems and the 5 aspects of CAD, including the degree of physical activity, the stability and frequency of angina, the degree of satisfaction of the treatment, and the perception of the disease. The higher the score, the better the quality of life and body function. SAQ will be measured at baseline and at the end of the 3-month intervention.

12. A record will be made of any side effects and possible adverse reactions arising from the intervention.

Safety measurements

All study participants are monitored weekly during the study intervention for the occurrence of adverse events defined by any undesirable experience. All adverse events that occur during the study will be recorded on the Adverse Event Case Report Form and will be evaluated for relevance to the intervention. All adverse events will also be reported to the Human Research Committee promptly in accordance with guidelines.

Only patients who are eligible and capable of completing the test will undergo a Cardiopulmonary Exercise Test (CPET). For enrolled patients meeting the rehabilitation training standards, they will be stratified according to the degree of motion risk and appropriate exercise intensity and time will be adjusted based on their risk stratification. Before the cardiac rehabilitation exercise, researchers will educate patients about the CHD rehabilitation exercises, including training contraindications and exercise advisories regarding the respective CER and TCCRP exercises. Moreover, the cardiac rehabilitation Center of Chinese PLA General Hospital, Beijing Shuili Hospital and Anzhen Community Health Service Center are equipped with a comprehensive set of rescue equipment. A thorough contingency plan and rescue procedure for cardiovascular events has also been formulated prior to the commencement of the research. Should an adverse event occur during the exercise, the researchers will immediately initiate the contingency plan to circumvent the occurrence of any fatal outcomes.

Data management and monitoring

Beijing Normal University will be responsible for managing the data and performing statistical analyses. The research assistants will be responsible for checking the integrity of the completed CRF and for timely entry of the collected data into the EpiData Manager, a free data management software. The project manager will be responsible for initial data cleaning, identifying, coding and converting the data into the proper format for analysis. All investigators involved in data management and analysis will be blinded to treatment allocation. Regular monitoring by the sponsor of China National Center for Biotechnology Development will be performed according to ICH GCP. China National Center for Biotechnology Development will be responsible for monitoring the research progress and meet every three months. It will oversee all aspects of the trial delivery including protocol amendments, recruitment of participants, monitoring intervention fidelity, management of timelines and milestones, publication and dissemination plans. Each amendment of the protocol conforms to the GCP principles and is submitted to the Ethics Committee for approval.

Statistical analysis

Continuous variables will be described as mean ± standard deviation (SD) for normal distributions or median for non-normal distributions, categorical variables will be described as frequency. Baseline data mainly describe the clinical characteristic and features of the subjects. We also tested the equalization of the two groups of variables. Continuous variables will be described as a two-sample Student's t-test for normal distributions or Wilcoxon test for non-normal distributions. Categorical variables will be described as the chi-square test. The group difference between intervention and control group at each time point (4 and 12 weeks after intervention or 12-week follow-up period) will be analysed using Student's t-test or Mann-Whitney U-test. A two-way analysis of variance with repeated measures will be used to determine the effects of time and group on our dependent variables. A Bonferroni-adjusted post hoc

analysis will be conducted when time-group interaction was detected. The analysis of primary or secondary outcomes will be based on an intention to treat (ITT) principle, and participants who either drop out from the study or fail to adhere to the protocol will have their last known data carried forward. The missing data will be imputed using a multiple imputation method. All data will be analyzed with SPSS 21.0 (IBM, Chicago, IL, USA) software packages. Statistical significance is defined as a two-sided P value < 0.05.

Adherence

To motivate participants' adherence, the research group will use several strategies (e.g. ancillary and post-trial care) to ensure the participants stays for the entire study period. (1) The participants will receive 36 cardiac rehabilitation treatments free of charge, for a total price of about 10,000 RMB; (2) the participants will be entitled specialist outpatient priority plus; (3) participants will be given three free face-to-face health education lectures by specialists; In addition, participant who complete the protocol successfully will be rewarded with Wushu training clothing no matter which group they belongs to. During the 3-month treatment period, participants will be asked to practice strictly according to the training program and will not be allowed to take part in any new or additional exercise programs. Throughout the 3-month intervention period, the researchers will track the number of missed sessions for each participant during the intervention period. Participants' attendance will be monitored during each in-person session by staff-completed attendance forms and class sign-in sheets. The percentage of compliance will be documented on the case report form. The rate of patient compliance = (total planned number of times − number of absence) / total number of times × 100%. A compliance rate of 80% or greater will be considered as good, whereas a compliance rate of less than 80% is considered as poor. An attendance of less than 20% will be considered as a dropout from the study.

Ethics and dissemination

This study conforms to the principles of the Declaration of Helsinki and relevant ethical guidelines. Ethical approval and informed consent form have been obtained from the Ethics Committee of Chinese PLA General Hospital (approval number: S2019-060-02). The study background and main objective as well as potential benefits and risks will be fully explained to the participants and their families. Findings from this study will be published and presented at conferences for widespread dissemination of the results.

DISCUSSION

The development of an ideal and effective cardiac rehabilitation program is still being explored and current cardiac rehabilitation mainly consists of contemporary conventional exercises. In fact, current cardiac rehabilitation programs have been reported to be underdeveloped and limited, reflected by a poor level of involvement with less than 30% of patients participating in the existing offerings.[29] As such, there is an unmet need for reforms and the provision of alternative cardiac rehabilitation programs to encourage the growth of cardiac rehabilitation. The exploration of an ideal cardiac rehabilitation exercise that is most beneficial for CCS patients should be determined.

This trial is the first one to compare the safety, feasibility and benefits of TCCRP and CER in CCS patients. There are several strengths of our trial: Firstly, the proposed research study is unique and the first study about a Bafa Wubu of Tai Chi which is a new Tai Chi school. Secondly, TCCRP in this study was specifically designed for patients with CCS. Finally, this is the first time for Tai Chi study to develop a comparative training system to match the conventional exercise. Our study will supply scientific evidence for the promotion of Bafa Wubu of Tai Chi at home and abroad.

TCCRP has some features which make it more suitable for CCS patients. Firstly, the intensity of TCCRP is low, and it is much safer for patients with CCS. Secondly, TCCRP is much easier to be learned and possesses a simple structure of movements, a

reasonable number of postures, and fewer practice environment limitations. Thirdly, TCCRP is not limited by location and easy to be carried out. Finally, TCCRP doesn't need money or any equipment. To sum up, compared with conventional exercise rehabilitation (CER), TCCRP is more suitable for CCS patients.

Compared with conventional exercise styles (e.g. aerobic, resistance, and extensibility exercise), Tai Chi typically involves a mind–body integration practice that combines the coordination of slow movements with mental focus, deep breathing, and relaxation for promoting both physical and mental well-being.[30-32] Previous studies have shown that regular Tai Chi exercise is beneficial in improving psychological and physiological outcomes among the elderly and various clinical populations (e.g. Parkinson's disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD) and psychological illness).[33-36] As a typical mind–body exercise which incorporates the characteristics of Traditional Chinese Medicine, Tai Chi may be considered to be an effective exercise to promote health in a diverse range of populations (e.g. healthy population, patients with chronic diseases, youths, middle-aged or elderly adults) .[37 38]

Compared with other Tai Chi schools, TCCRP has distinct advantages for CCS patients. TCCRP utilized Bafa Wubu of Tai Chi, namely, introductory routines to Tai Chi characterized by simple structures. Of the many styles of Tai Chi, however, it is hard to further popularize and generalize, due to its numerous movements and complexity, especially among patients with CCS. By upholding scientific, standardized and simplified principles, the Bafa Wubu of Tai Chi is systematically refined and sorted out on the basis of the other forms of Tai Chi, and the two exercise forms of "standing" and "marching", thus forming a set of Tai Chi routines for popularization characterized by culture, fitness and simplicity. Compared with the others, Bafa Wubu of Tai Chi is safer and much easier to be mastered for patients with CCS.

It should be acknowledged that this study has several limitations. It is difficult to monitor any additional physical activity of participants during the study duration.

Although all participants will be required to record their daily physical activity or exercise information with a pedometer, this is not sufficiently accurate to track their daily activity intensity. Furthermore, due to the nature of the exercise interventions (Tai Chi versus CER), the blinding of participants is unachievable in this trial. However, every effort will be made to ensure that the outcome assessors, data managers and statisticians participating in this study will be kept blind of the treatment allocations.

In conclusion, this study aims to assess the efficacy, safety and acceptability of an innovative TCCRP for CCS patients. The finding will be vital to help establish an optimal cardiac rehabilitation program for treating CCS patients.

TRIAL STATUS

This trial is currently in the recruitment phase. Estimated completion of the trial is expected to be completed by December 2020.

Additional files

Abbreviations

CHD: coronary heart disease; CCS: chronic coronary syndrome; ACS: acute coronary syndromes; TCCRP: Tai Chi cardiac rehabilitation program; TCM: Traditional Chinese Medicine; CER: conventional exercise rehabilitation.

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Authors' contributions

LSJ, MJ, and YHC conceived and designed the study protocol. The individual interviews were conducted by LSJ, MJ, LH, ZLS, and GAY. ZJW and MJ performed the translation and analysed the data. LSJ, ZJW, YW, CZH, WQY, CMZ, LYM, LYL, GTM, LCH, SB and WHW guided and supervised the Tai Chi training. ZJW and MJ contributed to writing and reading the manuscript. All authors approved the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

The data capture system and web servers will be provided by the data management center of Beijing Normal University (http://cas.bnu.edu.cn/cas/login) and the data management belongs to the Wushu and National Traditional Sports Culture Promotion Research Center of Beijing Normal University. The results of the review will be disseminated through peer-reviewed publications.

Open Access

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Table 1: Schedule for data collection; outcome measures per visits

Items	Phase I: Screening	Phase II: Baseline	Phase III: Month 1	Phase IV: Month 3	Phase V: Month 6
Inclusion/exclusion criteria	√				
Diagnostic index	√				
Signed informed consent	√				
Randomization and allocation	√				
Safety index	√	√	√	√	
General clinical information		√		√	
Primary outcomes		√		√	
Secondary outcomes		√		√	
Other indicators		√		√	
Recurrent cardiovascular events			√	√	√
Adherence			√	√	√
Adverse events			√	√	
Summary at the end of the study					√

Figure legend

Figure 1: Flow diagram of study design

SF-36 means the SF-36 Health Survey; CPSS means Chinese Perceived Stress Scale; NYHA means New York Heart Association; SAQ means Seattle Angina Scale; PSQI means Pittsburgh Sleep Quality Index; PHQ-9 means Patient Health Questionnaire-9; GAD-7 means Generalized Anxiety Disorder-7; BBS means Berg Balance Scale.

Figure. 2: Exemplary Bafa Wubu of Tai Chi; the pictures have taken the portrait right; the fugleman is the developer of TCCRP.

The “Bafa” consisted of eight hand techniques were shown in figure 2. Each figure showed each hand technique, namely “Peng (warding off), Lu (rolling back), Ji (pressing), An (pushing), Cai (pulling down), Lie (splitting), Zhou (elbowing) and Kao (shouldering)”.

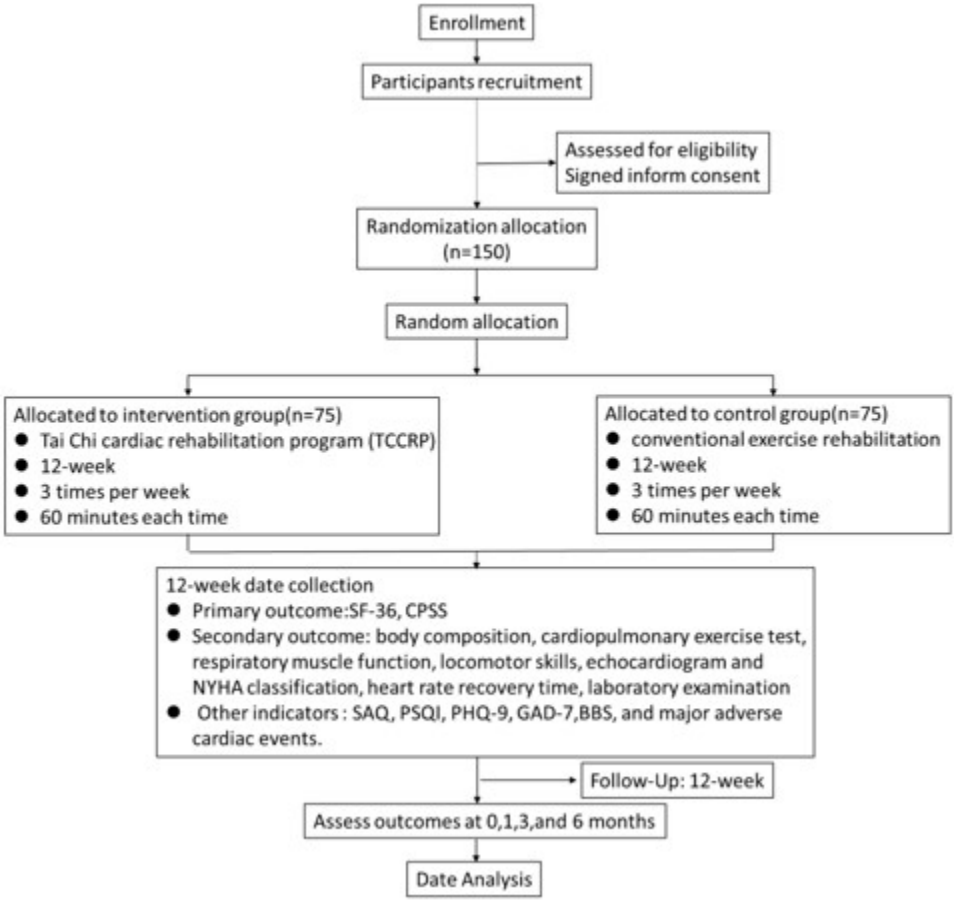

Figure 1: Flow diagram of study design

126x119mm (96 x 96 DPI)

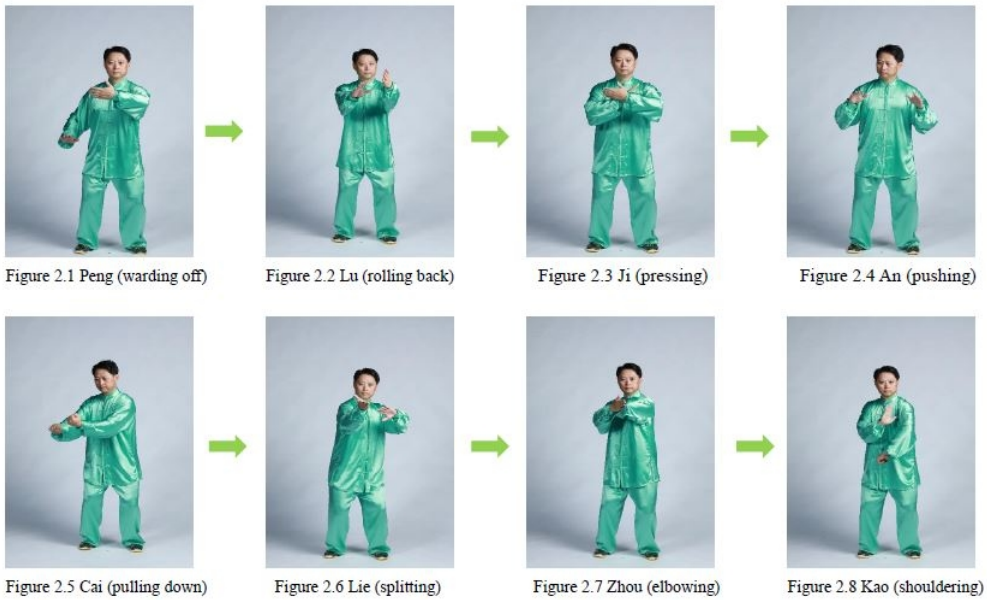

Figure. 2: Exemplary Bafa Wubu of Tai Chi; the pictures have taken the portrait right; the fugleman is the developer of TCCRP.

219x136mm (96 x 96 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title（P1）	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration（P7）	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version（P7）	3	Date and version identifier
Funding（P23）	4	Sources and types of financial, material, and other support
Roles and responsibilities（P22）	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale（P5, P6, P7）	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives（P6, P7）	7	Specific objectives or hypotheses

Trial design（P7）	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting（P9）	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria（P8, P9）	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions（P10, P11, P12, P13）	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes（P13, P14, P15, P16）	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline（P7）	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size（P7, P8）	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment（P9）	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation （P9）	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism （P9）	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation （P9）	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking) （P9, P10）	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods （P17）	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management （P17）	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods （P18, P19）	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring（P17, P18）	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms（P17）	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing(P18)	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval（P19）	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments(P18)	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent(P9)	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality（P17, P18）	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests（P23）	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data（P23, P24）	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care(P19)	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy（P20）	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials（P19）	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.