BMJ Open

Study design for a randomised controlled trial to explore the modality and mechanism of Tai Chi in the pulmonary rehabilitation of chronic obstructive pulmonary disease

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To cite: Fu J-J, Min J, Yu P-M, *et al*. Study design for a randomised controlled trial to explore the modality and mechanism of Tai Chi in the pulmonary rehabilitation of chronic obstructive pulmonary disease. *BMJ Open* 2016;**6**:e011297. doi:10.1136/bmjopen-2016-011297

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2016-011297).

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Received 27 January 2016
Revised 22 April 2016
Accepted 13 July 2016

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ABSTRACT

Introduction: Although pulmonary rehabilitation (PR) is associated with significant clinical benefits in chronic obstructive pulmonary disease (COPD) and has been recommended by guidelines, PR with conventional exercise training has not been widely applied in the clinic because of its inherent limitations. Alternative exercise such as Tai Chi has been investigated and the results are promising. However, the strengths and weaknesses of the exercise modality of Tai Chi, conventional PR and a combination of Tai Chi and conventional PR and the possible mechanisms underlying Tai Chi exercise remain unclear. This study aims to address the above research gaps in a well-designed clinical trial.

Methods and analysis: This study is a single-blind, randomised controlled trial. Participants with stable COPD will be recruited and randomly assigned to one of four groups receiving Tai Chi exercise, conventional PR using a total body recumbent stepper (TBRS), combined Tai Chi and TBRS, or usual care (control) in a 1:1:1:1 ratio. Participants will perform 30 min of supervised exercise three times a week for 8 weeks; they will receive sequential follow-ups until 12 months after recruitment. The primary outcome will be health-related quality of life as measured by the St George's Respiratory Questionnaire. Secondary outcomes will include 6 min walking distance, pulmonary function, the modified Medical Research Council Dyspnoea Scale, the COPD Assessment Test, the Hospital Anxiety and Depression Scale, the Berg Balance Scale, exacerbation frequency during the study period, and systemic inflammatory and immune markers.

Ethics and dissemination: Ethics approval has been granted by the Clinical Trial and Biomedical Ethics Committee of West China Hospital of Sichuan University (No TCM-2015-82). Written informed consent will be obtained from each participant before any procedures are performed. The study findings will be published in peer-reviewed journals and presented at national and international conferences.

Trial registration number: ChiCTR-IOR-15006874; Pre-results.

Strengths and limitations of this study

- Compare and contrast the feasibility and outcomes following three pulmonary rehabilitation interventions (Tai Chi, total body recumbent stepper (TBRS), a combination of Tai Chi and TBRS) using a robust randomised controlled trial design and methodology, and include a multidimensional assessment of chronic obstructive pulmonary disease (COPD) covering symptoms, quality of life, exercise capacity, functional and psychological status in the outcome measurement.
- A long-term follow-up will be conducted after the supervised intervention, in which comprehensive types of exacerbation will be recorded, and the extended benefits of Tai Chi will be examined.
- We will explore the potential mechanisms of Tai Chi therapy related to systemic inflammation and immunity, which has not been addressed in previous Tai Chi studies of COPD.
- Exclusion of the participants who are unable to tolerate the exercise during the run-in period or with co-occurring cardiovascular disease might affect the generalisation of study results in a 'real world' setting.
- The cultural contexts and healthcare settings might limit the applicability of Tai Chi in other countries and populations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by incompletely reversible airflow obstruction and airway inflammation and is associated with a variety of systemic consequences. Skeletal muscle dysfunction is an important systemic manifestation, along with dyspnoea, which results in reduced physical activity, exercise tolerance and quality of life in patients with COPD.[1] Robust evidence supports

incorporation of pulmonary rehabilitation (PR) into COPD management. PR is a comprehensive and individualised intervention with education, behaviour change and exercise training as the core component. PR addresses the systemic effects of COPD and has been clearly demonstrated to reduce daily symptoms and improve exercise capacity and quality of life.[2]

Although the benefits of conventional PR in COPD are well established, patients have limited access to this intervention because of the cost and limitations of staff and equipment, even in developed countries.[3 4] Therefore, alternative exercise has been investigated in an attempt to overcome these barriers. Tai Chi has great potential because it addresses limitations related to time and venue as well as the medical cost of standard PR; Tai Chi could also be a community- or home-based practice.

Tai Chi is a traditional Chinese mind–body exercise consisting of balance, posture alignment, weight shifting, circular movements, relaxation and breathing control.[5] Many studies have shown the potential beneficial effects of Tai Chi on various clinical conditions such as hypertension, osteoarthritis and cardiovascular disease (CVD).[6] Several meta-analyses have confirmed the therapeutic value of Tai Chi in COPD, in which it was associated with improved quality of life, physical performance and psychological status.[7–12]

However, we observed that the above conclusions could only be made based on comparison with a non-exercise or breathing training arm. We searched the literature using the terms 'randomised clinical trials', 'chronic obstructive pulmonary disease' and 'Tai Chi' in Medline, EMBASE and PubMed databases, as well as the Chinese databases, CNKI and Wanfang, and 13 randomised controlled trials were identified up to 31 July 2015 (table 1). In these studies, Tai Chi exercises were compared with either usual care or breathing training, except for the study by Ng *et al*.[22] Therefore, although either Tai Chi[7–12] or conventional PR[2] alone has been demonstrated to be beneficial in COPD, there are still many unknowns about how to better solve current clinical problems, such as how Tai Chi compares with conventional PR in terms of its pros and cons in COPD, if it is possible for Tai Chi to replace conventional PR, which modality of Tai Chi provides the maximum benefit to patients with COPD, and how to compensate for the limitations of conventional PR.

In terms of the mechanisms of the therapeutic effects of Tai Chi, an increasing number of studies have revealed that Tai Chi can affect inflammatory processes and immune responses in clinical populations and healthy controls. Tai Chi is associated with decreased circulating C-reactive protein (CRP) and interleukin (IL)-6 levels in patients with certain clinical conditions and in healthy people with elevated inflammatory markers at baseline.[26 27] Upregulated systemic inflammation is the hallmark of the inflammatory response in COPD, linked to systemic consequences and comorbidities,[28] and it is also related to the disease prognosis—for example, lung function decline and future exacerbations.[29] The mechanisms underlying the therapeutic effects of Tai Chi in COPD are unknown. It is unclear if Tai Chi affects the level of systemic inflammatory markers in COPD that contribute to the clinical benefits from participating in Tai Chi.

Table 1 Randomised controlled trials of Tai Chi in chronic obstructive pulmonary disease

First author	Year	Tai Chi arm	Control arm
Chan[13]	2010	Modified 13-form Yang style	Breathing exercise and self-paced walking
Chan[14]	2011	Modified 13-form Yang style	Breathing exercise and self-paced walking
Chan[15]	2013	Modified 13-form Yang style	Self breathing and walking exercise; usual care
Du[16]	2013	Modified 24-form Yang style	Breathing exercise and walking
Du[17]	2013	Modified 24-form Yang style	Breathing exercise and walking
Gu[18]	2012	Modified 24-form Yang style	Usual care
Leung[19]	2013	Sun style	Usual care
Li[20]	2012	Modified 24-form Yang style	Breathing exercise
Niu[21]	2014	Not mentioned	Usual care
Ng[22]	2014	5-form Sun style plus conventional PR	Conventional PR
Wang[23]	2014	Modified 24-form Yang style	Usual care
Yao[24]	2004	Chen style	Breathing exercise
Yeh[25]	2010	Short-form Yang style	Usual care

PR, pulmonary rehabilitation.

Ng *et al*[22] conducted a study combining Tai Chi with conventional PR and found that this integrated approach might have a modest complementary benefit for exercise capacity compared with conventional PR alone. However, greater disease severity and greater compliance with exercise in the Tai Chi group might affect the interpretation of the study findings, and how this approach compares with pure Tai Chi training is unclear. Therefore, we will conduct a randomised, single-blind clinical trial comparing the exercise modalities of Tai Chi, conventional PR, and an integrated approach of Tai Chi and PR in COPD to examine (1) the differences in the therapeutic effects on COPD in terms of various clinical outcomes and (2) the potential mechanisms of Tai Chi related to systemic inflammation and immunity in COPD.

METHODS

Design

This is a parallel, single-blind, randomised controlled clinical trial. Participants will be enrolled from the West

China Hospital, Sichuan University of China. The study protocol has been registered with the Chinese Clinical Trial Registry (ChiCTR-IOR-15006874). Participants will be randomly assigned to one of four groups: Tai Chi, conventional PR using total body recumbent stepper (TBRS), a combination of Tai Chi and conventional PR, and a control group. The study procedure is shown in figure 1. A 1-week run-in period has been designed to precede randomisation; during this period, participants will receive education and training in both Tai Chi and TBRS exercises to exclude individuals who are not able to tolerate the exercises and to enhance study compliance. Outcome measures will be repeated at baseline, at the end of the supervised rehabilitation programme (8 weeks), and during the follow-up until 12 months after the baseline visit (table 2).

Participants

Patients with COPD in our clinical database will be invited; other recruitment resources include advertisements in West China Hospital, Chengdu, China and community hospitals. Potential participants will be contacted by phone to assess their basic eligibility for the study. Individuals interested in the study who also meet the basic eligibility criteria will be scheduled for a screening visit and the informed consent process.

The diagnosis of COPD will be confirmed in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[30] Participants will be included if they: (1) are diagnosed with COPD; (2) have moderate to severe COPD as defined by ≤30% post-bronchodilator forced expiratory volume in 1 s (FEV_1) <80% predicted; (3) are between 45 and 75 years of age; (4) are clinically stable, confirmed by the absence of using systemic corticosteroids and/or antibiotics, emergency room (ER) visits or hospitalisations in the past 4 weeks;[31] (5) are willing to give written informed consent. The exclusion criteria will be: (1) GOLD stage 4 defined by post-bronchodilator FEV_1 <30% predicted; (2) coexistence of other chronic respiratory disorders;

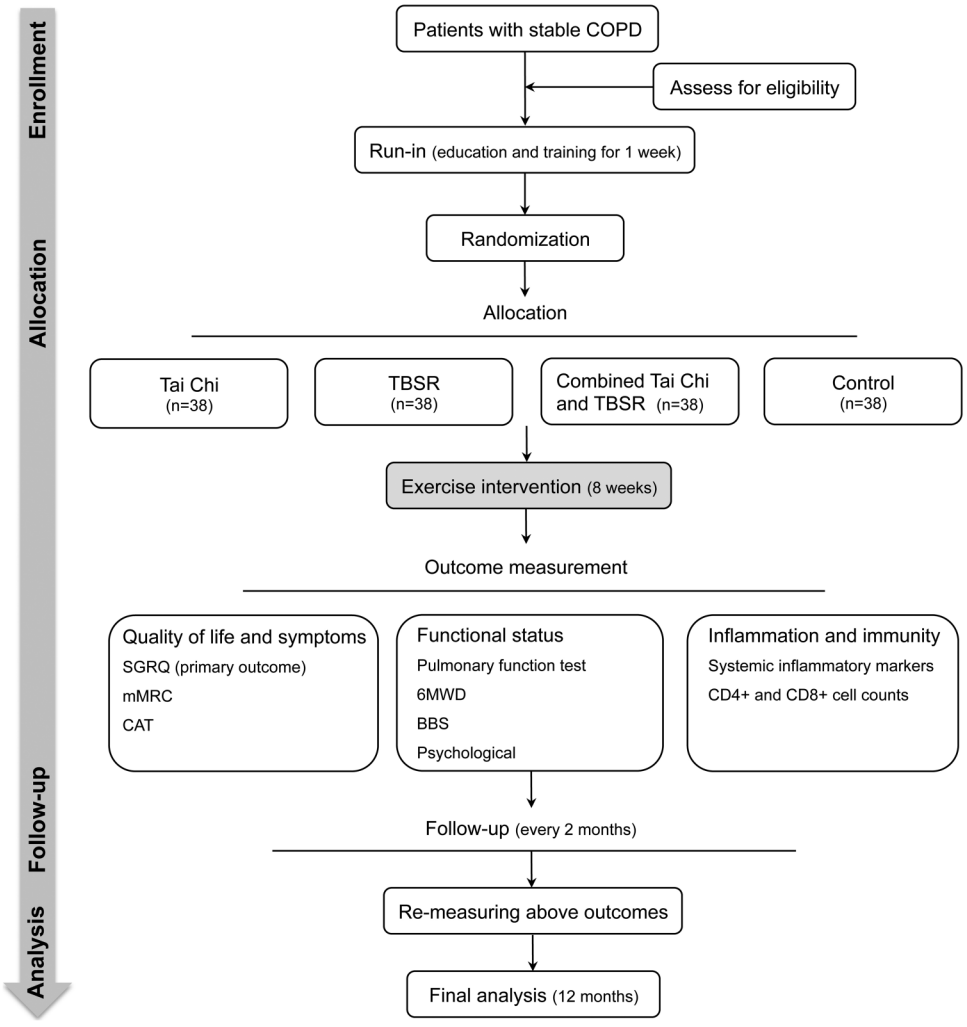

Figure 1 Study flow chart. 6MWD, 6 min walk distance; BBS, Berg Balance Scale; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council Dyspnoea Scale; SGRQ, St. George Respiratory Questionnaire; TBRS, total body recumbent stepper.

Table 2 Outcome measurement during rehabilitation programme and follow-up

Visit measures	Visit 1 Baseline	Visit 2 2 months	Visit 3 4 months	Visit 4 6 months	Visit 5 8 months	Visit 6 10 months	Visit 7 12 months
Medical history and treatments	×						
SGRQ	×	×	×		×		×
Symptom severity (mMRC, CAT)	×	×	×	×	×	×	×
6MWT	×	×	×	×	×	×	×
HADS	×	×	×	×	×	×	×
Spirometry	×	×	×	×	×	×	×
Blood taken	×	×			×		×
Exacerbations	×	×	×	×	×	×	×

6MWT, 6 min walking test; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety and Depression Scale; mMRC, Modified Medical Research Council Dyspnoea Scale; SGRQ, St George's Respiratory Questionnaire.

(3) presence of severe comorbidities such as haematological or solid organ malignancy, symptomatic CVD, musculoskeletal or neurological disease that might affect ambulation or exercise training; (4) cognitive dysfunction, metal disorder or abnormal behaviours; (5) participation in a PR programme in the past 12 months; (6) currently practising Tai Chi or participating in a clinical trial of COPD and other diseases.

Randomisation and blinding

After a screening visit that will assess the eligibility and run-in period, participants will be randomly assigned to one of the following four groups in a 1:1:1:1 ratio: Tai Chi, TBRS exercise, a combination of Tai Chi and TBRS, and usual care (control) groups. Random numbers will be obtained using the PRCO PLAN random-number generator from SAS V.6.1 by a professional statistician. The allocation sequence will be kept in sequentially numbered, opaque and sealed envelopes. The main investigator and data analyst will not be involved in any interventions and will be blinded to group allocation. Outcome assessors evaluating the effects of the treatments will also be blinded to the allocation of treatments. Participants, research physiotherapists and Tai Chi instructors who supervise the exercise will not be blinded to the allocation. Once allocation has taken place, the research physiotherapists and Tai Chi instructors will receive a copy of the participant number and allocation, and the outcome assessor will be informed of the participant number only. To maintain observer blindness throughout the study period, participants will be requested not to discuss the intervention with the outcome assessors.

Sample size

The sample size calculation of this study is based on the St George's Respiratory Questionnaire (SGRQ) total score in the study by Chan *et al*.[15] By computing the changes in the SGRQ total score in the Tai Chi group and in the self-practice group (breathing and self-pacing walking exercise) before and after the interventions, we found that 25 participants per group would be required to achieve a power of 0.8 and a significance level of 5% for difference detection. Furthermore, we conducted a power analysis using the fpower function in Stata V.13.0 to estimate the sample size needed to perform four-group comparisons provided that an α is set as 0.05. The results showed that recruitment of 25 participants would achieve a statistical power of 0.74, and 30 participants would achieve a power of 0.83. A sample size of 38 participants per group, inclusive of a 20% dropout compensation,[32 33] will be used for this trial. Therefore, 38 participants per group and a total of 152 participants is a reasonable sample size for this study.

Intervention

A finger pulse oximeter will be placed on each participant for continuous use during exercise to monitor oxygen saturation and heart rate (HR) for exercise intensity monitoring and safety. The resting HR and oxygen saturation will be recorded before exercise. Each class will last for 30 min, and participants in the three exercise groups will participate in the rehabilitation programme three times a week for 8 weeks for the same amount of exercise time and at the same frequency.

We will conduct training sessions with all the staff involved in the study including research physiotherapists for TBRS training, Tai Chi instructors and outcome assessors to thoroughly review the concepts of COPD and the standardised protocols for training and outcome assessments at the beginning of the study and as needed throughout the course of the study. All sessions will be monitored regularly and feedback provided throughout the study to ensure proper instruction.

Yang-style Tai Chi, in its many variations, is the most popular and widely practised in the world; therefore participants allocated to the Tai Chi group will undergo the simplified 24-form Yang-style Tai Chi training at the rehabilitation centre of the hospital. The 24-form Yang-style Tai Chi consists of 24 standard movements as described in box 1 and figure 2A. The certified Tai Chi instructor will explain and demonstrate the Tai Chi principles and the practising techniques and safety precautions of each movement at the beginning of the study; the instructor will review these principles and techniques as needed throughout the course of the

Box 1 Standard movements of 24-form Yang-style Tai Chi

Name of the movements
1. Initiation
2. Parting the wild horse's mane (3×)
3. White crane spreads its wings
4. Brush knee (3×)
5. Hand strums the lute
6. Step back and repulse monkey (4×)
7. Grasp the sparrows's tail (left)
8. Grasp the sparrows's tail (right)
9. Single whip
10. Cloud hands (3×)
11. Single whip
12. High pat on the horse
13. Heel kick (right)
14. Strike tiger's ears
15. Heel kick (left)
16. Snake creeps through grass, rooster stands on one leg (left)
17. Snake creeps through grass, rooster stands on one leg (right)
18. Fair lady works the shuttles (right and left)
19. Needle at the sea bottom
20. Fan through the back
21. Turn, deflect, parry and punch
22. Apparent close-up
23. Cross hands
24. Closing

study. An instructor will always practice with the participant to demonstrate and correct the Tai Chi movements. Participants will also be instructed to focus and perform traditional Tai Chi breathing, such as along breathing, against breathing, Dan Tian breathing (deep abdominal breathing) and whole body breathing methods, together with the body movements.

The conventional rehabilitation exercise in this study will use a TBRS (Humaneotec, Guangzhou, China) (figure 2B). A research physiotherapist will educate the participant about the equipment, exercise protocol, termination criteria and emergency notice before the start of exercise. Once the participant is seated in the TBRS, necessary adjustments will be made for leg and arm length according to the methods used by Billinger *et al*.[34] The participant will be instructed to place arms and feet in the desired position, pushing or pulling the upper arm grips and pedalling simultaneously. The exercise protocol will start at a stepping cadence of 40–60 steps/min.

In the combined exercise group, the participant will start with TBRS exercise lasting for 15 min, followed by 15 min of Tai Chi exercise.

Participants in all study groups will continue with their usual medical care during the full study period. Participants in the control group will not perform PR but can maintain their home-based exercise with the consideration that a small number of patients with COPD in China have access to PR.

Monitoring of exercise intensity

To design a controlled trial with comparable exercise intensity in different exercise groups, the participants' HR and oxygen saturation will be monitored while they practise a full set of exercises. Previous reports[19 35] have demonstrated that Tai Chi is exercise of moderate intensity. The COPD rehabilitation guideline[36] recommends moderate intensity to ensure effective exercise. The research physiotherapists or Tai Chi instructors will supervise and prompt participants to achieve moderate exercise intensity. In the Tai Chi group, participants will also be asked to imagine pushing against resistance

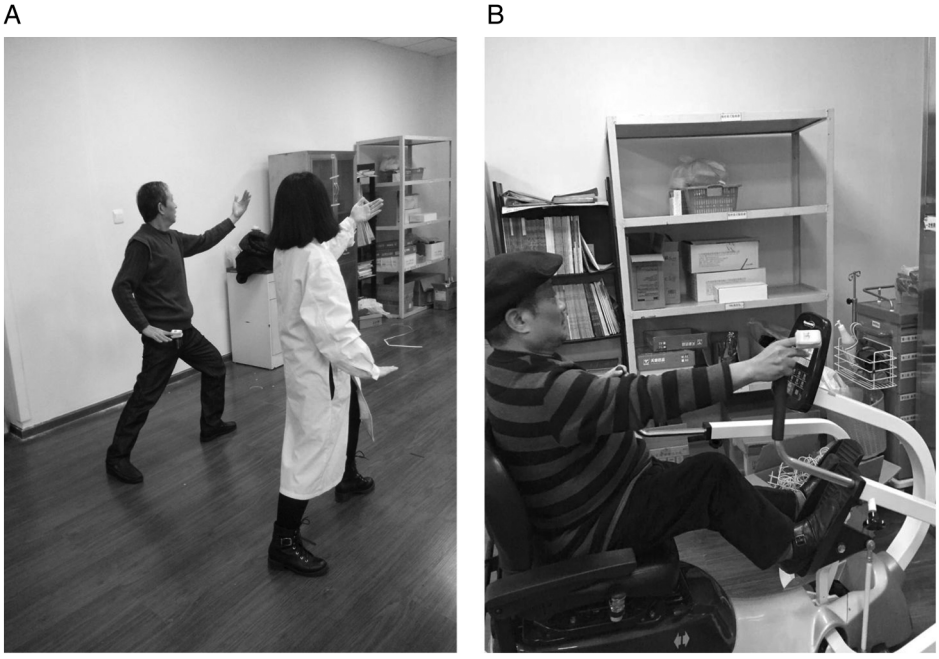

Figure 2 Illustration of the exercises (A) of Tai Chi and (B) with the total body recumbent stepper.

during movements, to squat lower, or to take larger steps in certain movements to increase exercise intensity. Participants in the TBRS group will be instructed to speed up and/or increase resistance to achieve the exercise intensity. For moderate exercise intensity, a target HR of between 40% and 59% of the HR reserve (HRR) is required according to American College of Sports Medicine criteria.[37] For individuals taking β-blockers, the rate of perceived exertion using the Borg 6–20 scale will be applied to achieve target exercise intensity; a score of 12–14 is categorised as moderate-intensity exercise.[38] The formula to calculate a target HR is given as follows:[37]

$$\text{Target HR} = ((220 - \text{age}) - \text{resting HR}) \times \%\,\text{HRR} + \text{resting HR}$$

COPD-related education

Participants in all four groups will receive the same weekly educational sessions. The contents include smoking cessation, diagnosis, COPD medications, action plan, exacerbations, nutrition and self-management, such as infection prevention, inhalation technique, breathing and coughing techniques.

Outcome measurement

Primary outcomes

St George's Respiratory Questionnaire

The SGRQ is a 50-item questionnaire developed to measure the health-related quality of life in patients with obstructive airway disease.[39] The result of this questionnaire is presented as a total score, as well as three subscores of symptom, impact and activity. Study researchers will review the *Guide to Completing the SGRQ* before seeing participants to prepare for their questions. Participants will be asked to complete the questionnaire as honestly as possible and to give the most applicable answers to the questions; questions may be read to participants with reading difficulties.

Secondary outcomes

Severity of symptoms

The symptom burden is an important domain of COPD measurement and constitutes one of the components of the severity classification grade of COPD in the updated GOLD document.[30] The Modified Medical Research Council Dyspnoea Scale (mMRC) is a five-point (0–4) scale based on the severity of dyspnoea and is an index associated with COPD mortality. The COPD Assessment Test (CAT) is a patient-completed questionnaire that contains eight questions covering domains relating to the impact of COPD symptoms including cough, sputum production, chest tightness, exercise capacity, sleep quality and energy level beyond a single assessment of breathlessness.

Pulmonary function tests

Pulmonary function tests (PFTs) will be undertaken by the outcome assessors, who maintain a high level of proficiency and are certified to perform PFTs following the American Thoracic Society standards to ensure optimal results. Participants will withhold bronchodilators for their duration of action before the tests. Three reproducible measurements of FEV_1 and forced vital capacity will be obtained (Medgraphics MGC Diagnostic Corporation, St Paul, Minnesota, USA) before and after the inhalation of 400 µg salbutamol via a metred dose inhaler with a valved holding chamber (Taian Character Polymer Co, Taian, China). The predicted values are referred to the Intermountain Thoracic Society[40] for Asian populations.

6 min walking test

The 6 min walking test (6MWT) is one of the most widely used tests to assess exercise tolerance in chronic respiratory disease and heart failure. Participants will be administered 400 µg salbutamol 20 min before the walking tests. The 6 min walk distance (6MWD) will be measured using the best of two 6MWTs according to the American Thoracic Society guidelines.[41]

Berg Balance Scale

The Berg Balance Scale is a 14-item scale designed to measure static and dynamic balance abilities of older adults during a series of predetermined tasks.[42] The ability to maintain stability and balance is indispensable for independent activities of daily living, mobility and for avoiding falls. Impaired balance is associated with an increased risk of falls, resulting in higher mortality.[43] Previous reports have demonstrated a significant deficit in balance control in patients with COPD,[44] which is probably due to age and various comorbidities. Participants will be given instructions to complete a movement or maintain a position for a specific time, and researchers will score each task according to the performance and use of support.

Psychological status

The Hospital Anxiety and Depression Scale (HADS) is a self-administered measure used to screen for the presence of depression and anxiety and has been shown to be a valid and reliable measure of the severity of an emotional disorder used in a general hospital practice.[45] Participants will be instructed to choose the one response from the given answers that best describes their current feelings.

Inflammatory mediators and immune function

To examine the effects of the various formats of exercise on systemic inflammation, which is an important component of COPD pathogenesis and is related to disease progress and comorbidity,[29 46] the systemic inflammatory mediators IL-6, CRP, IL-8 and tumour necrosis factor (TNF)-α will be assayed. In addition, cell-mediated immunity represented by CD4 and CD8 counts will be determined.

Follow-up and exacerbation frequency

The participants will be required to attend the clinic every 2 months after the 8-week classes for 12 months after the first visit. Outcomes will be retested according to the visits to track their changes or declines after rehabilitation (table 2). The participants will not be required to maintain the exercises they started in the classes, although they will be asked to record the format, intensity and frequency of their exercise in a daily diary following the intervention. Strategies to optimise participant retention and complete follow-up have been developed as follows: (1) involve well-trained research personnel and provide training to study staff with tips for educating and motivating the participants; (2) provide study-specific education to the participants; (3) involve the family or caregivers of the participants; (4) schedule appointments in advance and send reminders; (5) offer visits after work hours or at weekends; (6) allow rest between tests as needed. If the participant fails attend the follow-up visit, the completion of questionnaires via telephone or email will be allowed to achieve as much as the measures.

Respiratory hospitalisation, ER visit, unscheduled outpatient visit, and medication use including antibiotics and systemic corticosteroids will be recorded at each follow-up visit. An exacerbation of COPD is defined as a COPD-related episode that leads to (a) hospitalisation or (b) an ER visit or (c) the need for oral corticosteroids and/or antibiotics for at least 3 days.[31]

Statistical analysis

The data will be analysed using Stata V.13.0. Mean (SD) or median (IQR (25–75%), q1–q3) will be used depending on the data distribution. A paired t-test or Wilcoxon signed-rank test will be performed to compare the outcomes at baseline with those after 8 weeks of classes and during the follow-up within a group. Analysis of covariance will be used to compare the results of post-rehabilitation and follow-up visits between groups, with the corresponding baseline value as a covariate. Pairwise comparisons between the intervention arms will be performed using Tukey's HSD post hoc test.[47] Intention-to-treat analysis will be applied to include all randomised participants, and the missing data will be analysed according to the last-observation-carried-forward rule. $p<0.05$ will be defined as significant. Sample size calculation and power analysis was performed using the fpower function in Stata V.13.0, where type I and type II errors will be set to be 0.05 and 0.8, respectively. The treatment effect of different exercise modalities on continuous outcomes will be measured by the difference in the means and compared with minimal clinically important differences to determine the clinical importance.[48]

Safety

Supervised stretching will be performed before and after exercise. Oxygen saturation and HR will be continuously monitored during exercise. An increase in HR to ≥80% of HRR or fall in oxygen saturation to <85% will lead to slowing down or ceasing of exercise. Any adverse effects such as dizziness or fainting, extreme breathlessness, chest pain, severe muscle pain or cramps, falls or loss of consciousness during exercise or after a class will be documented and will be assessed by study staff to decide if the event is related to exercise programmes and is reportable. In the occasion of a severe adverse event, investigators will be asked to record and report to the trial applicant and the ethics committee within 24 hours, and participants will receive appropriate treatment.

Data and specimen management

The participant's identity, medical records and the data collected relating to the study will remain confidential information. Participants will be identified for the purposes of the study by initials and an assigned participant trial number. Study-related information will be stored securely at the study site for 10 years in locked filing cabinets in areas with limited access. Only authorised research assistants will have access to the final trial dataset. Blood samples will be processed and stored according to their specific requirements in our laboratory for the assessment of systemic inflammatory and immune markers.

Ethics and dissemination

This trial is being conducted in accordance with the Declaration of Helsinki.[49] The Clinical Trial and Biomedical Ethics Committee of West China Hospital of Sichuan University approved the study (TCM-2015-82). All participants will be volunteers, and a written informed consent form will be signed. Participants will be able to cease their involvement in the study at any time. If there are any changes to the protocol during the course of the study or on annual renewal, an amendment will be submitted to the institutional review board for approval. The findings will be disseminated through academic presentations, peer-reviewed publications and by means of a national seminar at the end of the study.

DISCUSSION

Patients with COPD are characterised by the symptom of dyspnoea and by impaired exercise capacity. The chronic sensation of dyspnoea is one of the most common symptoms in COPD and is invariably present in all severity stages either at rest or under conditions of exercise. The mechanisms of dyspnoea and exercise intolerance in COPD are complex and multifactorial.[50] Exercise capacity is often limited by dyspnoea, whereas exertional dyspnoea is partly a reflection of peripheral muscle dysfunction.[36] Exercise training is the best available means of improving muscle function in COPD and is considered the cornerstone of PR.[36] PR has been clearly demonstrated to improve quality of life, reduce

dyspnoea symptoms and increase exercise capacity in patients with COPD.[51]

A symptom is an individual's consciously appreciated sensation of a physiological problem and is the result of an interaction of multiple physiological, psychological, social and environmental factors that affect the quality and intensity of the perception of the symptom.[52] In COPD, strategies for the relief of dyspnoea can be physiological or cognitive/behavioural. The rationale underlying the use of cognitive/behavioural strategies is that there is an interaction between the mind and body and that individuals can be taught new patterns of thinking, feeling and behaving to cope with symptoms.[53] A previous study has shown that yoga training was associated with significant symptomatic improvement in dyspnoea along with an improvement in exercise tolerance.[54] Tai Chi is an ancient Chinese martial art and exercise; its inherent features of isometric exercise, stretching, relaxation and body posture correction combined with breathing techniques provide a typical mind–body exercise therapy for various diseases.[9] An increasing number of studies are attempting to explore the possibility of using this 'old exercise' for a 'novel use' in the treatment of COPD. The results appear to be quite promising; Tai Chi exercise has significant therapeutic effects on quality of life and exercise capacity and has an uncertain benefit on lung function based on several meta-analyses[7 10 11] (figure 3). However, the above conclusions are drawn only in comparison with non-physical exercise or breathing training, which is mostly completed at home (table 1). The benefits of Tai Chi might partially come from the muscle strength and balance exercises; however, the components of mindfulness and breathing techniques in Tai Chi, which are not a required part of standard PR, may also contribute to the improvement in chronic dyspnoea. How Tai Chi compares with conventional PR in terms of improvement in patient-centred outcomes, including quality of life and severity of symptoms and other objective measures, is unknown (figure 3). Therefore, in this study, we designed two parallel groups of Tai Chi and conventional PR to compare their effects in COPD.

Conventional PR is characterised by exercise training to improve aerobic capacity and muscle strength. As one of the cognitive–behavioural therapies, Tai Chi exercise combines mindfulness and breathing control with functional movements. It is possible that the combination of these two exercise modalities would have complementary effects compared with Tai Chi or conventional PR alone on the clinical outcome of COPD including the severity of dyspnoea. This study will examine the effect of an exercise modality incorporating Tai Chi into conventional PR on COPD outcomes.

Tai Chi has the advantage of being convenient and easily implementable and could be performed at a local community centre or at home. Evidence drawn from systematic reviews revealed inconsistent results in terms of the comparison between hospital-based versus community-based rehabilitation on quality of life:[2] hospital-based rehabilitation was associated with greater improvements in all domains of the Chronic Respiratory Questionnaire (CRQ), although the SGRQ showed no difference. Although the three types of exercise will all be supervised and completed in the hospital in our study, the findings might also provide information on the possibility of Tai Chi as a community- or home-based exercise requiring no special equipment, and this possibility deserves further study in the future.

Increasing evidence indicates that COPD is a complex disease characterised by airflow obstruction and airway inflammation. Systemic consequences and a variety of comorbidities are also involved. These systemic consequences and comorbidities include exercise intolerance, skeletal muscle dysfunction, metabolic dysfunction,

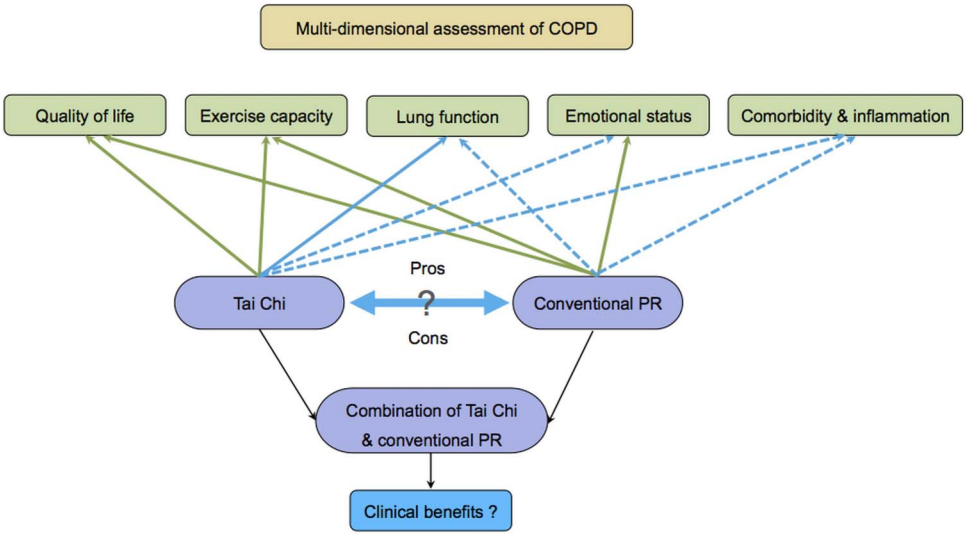

Figure 3 Evidence and research gaps in previous studies of Tai Chi and conventional pulmonary rehabilitation (PR) in chronic obstructive pulmonary disease (COPD): green arrows with solid line represent confirmed associations; blue arrow with solid line represents uncertain association; blue arrows with dotted line represent unknown associations.

osteoporosis, CVD and excess mortality.[28] The mechanisms of these systemic manifestations are unclear, although systemic inflammation is hypothesised to be of predominant importance. Systemic inflammation is defined as elevation of proinflammatory cytokines or acute-phase reactants in the circulation.[55] CRP and IL-6 are classic mediators representing the level of systemic inflammation in various diseases including COPD,[1 56] and our previous studies demonstrated the presence and their important role in COPD.[57] TNF-α and IL-8 are also crucial proinflammatory cytokines involved in the systemic inflammatory response in COPD.[1 58 59] A variety of mind–body exercises, including Tai Chi, have been shown to be associated with decreased inflammatory markers such as CRP,[26] monocyte-induced inflammation and immune regulation[60] in different clinical populations.[27] However, the effect of Tai Chi on the levels of circulating inflammatory mediators in patients with COPD remains unclear. Given the benefits of Tai Chi on COPD and on other diseases—for example, osteoporosis and CVD, which are the most commonly observed comorbidities of COPD—it is possible that the suppression of systemic inflammation might be one of the mechanisms underlying the treatment effects of Tai Chi in COPD. Therefore, we will test the above hypothesis by examining the levels of these biomarkers before and after treatment inventions during the study.

In the absence of any maintenance strategy, the benefits of PR in terms of the 6MWD and quality of life declined after a standard PR programme but the improvements remained significant after 1 year.[61] The duration of the long-term maintenance of the benefits from Tai Chi has not been investigated, and we will address the question in the 12-month follow-up study. Although the previous study did not find an association between conventional PR and hospitalisation rate in stable COPD,[61] we will record more comprehensive types of exacerbation including hospitalisations, ER visits, access to outpatients and changes in maintenance therapy prescribed by doctors or self-administered in this study.

There are several highlights of this study. We will compare the exercises of Tai Chi and conventional PR for the first time to investigate the pros and cons of the two rehabilitation strategies. For the conventional PR group, TBRS combining upper- and lower-extremity training will be used, which has been shown to be a preferred exercise for older adults[62] and is recommended in an official statement.[51] In addition, an exercise modality that integrates the components of mindfulness, breathing control and upper and lower extremity muscle training of Tai Chi and conventional PR will be examined. Moreover, a regular follow-up will be conducted to investigate the long-term benefits of Tai Chi exercise, in which comprehensive types of exacerbation will also be recorded. In the outcome measurements, we will include multiple dimensions of COPD assessments covering symptoms, quality of life, exercise capacity, and functional and psychological status. We will examine the potential mechanisms of different exercise modalities related to systemic inflammation and immunity; this topic has not been addressed in previous Tai Chi studies of COPD.

This study has some limitations that should be considered. Although the sample size calculation was conducted based on previous studies, the study findings will need to be confirmed with a larger number of patients. CVD is among the most important comorbidities observed in COPD. We will exclude patients with symptomatic CVD for safety, although it has been shown that patients with CVD benefit from rehabilitation programmes.[9] Although previous studies have shown that PR is generally well tolerated in patients with severe COPD,[63] patients with very severe lung function impairment and those who are unable to tolerate the exercise during the screening and run-in period will be excluded because of considerations of safety and compliance. The exclusion might affect the generalisation of study results to populations in a 'real world' setting. Our rehabilitation protocols are not identical with other Tai Chi studies; however, the frequency and exercise intensity in this trial is comparable with previous studies of COPD rehabilitation and meet the requirements recommended in an official statement.[51] A prior study found that patients in a Tai Chi group tended to show increased compliance with home exercise;[22] therefore, home exercise will be documented in a patient diary. The cultural contexts and healthcare settings might limit the applicability of Tai Chi in other countries and populations.

CONCLUSION

This article presents the design and protocol of a clinical trial investigating the effects of Tai Chi exercise in patients with stable COPD. The results of this innovative study are expected to provide answers to the following questions. What are the advantages and limitations of Tai Chi compared with conventional PR in COPD in terms of a variety of outcomes? Would Tai Chi affect systemic inflammation and immune functions that are potentially involved in the mechanisms of its therapeutic effects in COPD? Would an exercise modality combining Tai Chi and conventional PR be a superior approach to Tai Chi rehabilitation in COPD? The study findings will provide evidence and novel insights into the rehabilitation strategy of Tai Chi in COPD.

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Acknowledgements The authors acknowledge Wei Xiao and Dao-Hong Chen for assistance with the development of the case report form and the ethics application, and Jing-quan Li and Yi Pan for professional advice on and teaching and supervision of Tai Chi exercise.

Contributors JJF participated in the study design and drafted the manuscript. JM contributed to the trial registration, ethics application and study design. PMY participated in the development of the TBRS protocol, exercise intensity and safety-monitoring protocols. VMM contributed to the selection of outcome measurement and study design. BM participated in the study design, protocol development and interpretation, and reviewed the manuscript. All authors read and approved the final manuscript.

Funding This trial is financially supported by the Key Project of Applied Science and Technology of Sichuan Province, China (approval number: Office for Talent Resource, Sichuan Province [2015]-2-4). The funder will not be involved in the conduct or interpretation of this trial, or in any decision to publish the results.

Competing interests None declared.

Ethics approval The Clinical Trial and Biomedical Ethics Committee of West China Hospital of Sichuan University, China.

Provenance and peer review Not commissioned; externally peer reviewed.

Trial status The trial was registered in August 2015 and is currently in the recruitment and pre-results phase. The results of this study will be available in 2017.

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Study design for a randomised controlled trial to explore the modality and mechanism of Tai Chi in the pulmonary rehabilitation of chronic obstructive pulmonary disease

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BMJ Open 2016 6:
doi: 10.1136/bmjopen-2016-011297