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Traditional Chinese exercise in a contextually adapted cardiac rehabilitation program for chronic heart failure

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Traditional Chinese Exercise in a Contextually Adapted Cardiac Rehabilitation Program for Chronic Heart Failure
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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This thesis is dedicated to my parents.

ABSTRACT

Background: Exercise-based cardiac rehabilitation (EBCR) is a therapy which benefits patients with chronic heart failure (CHF). The delivery of EBCR should adopt an evidence-based approach, as well as be culturally appropriate and sensitive to individual needs and preferences. The *Baduanjin* Eight-Silken-Movements wIth Self-Efficacy building for Heart Failure (BESMILE-HF) program is a contextually adapted cardiac rehabilitation program. It uses a traditional Chinese exercise, *Baduanjin* , to solve the unmet demand of EBCR programs due to their scarcity and unaffordability in China.

Aim: The overall aim was to provide knowledge, experience, and evidence on how to effectively deliver a contextually adapted EBCR program for patients with CHF in China or other similar settings where EBCR services are scarce.

Methods: To evaluate the current evidence on traditional Chinese exercises (TCEs) regarding their rehabilitation effects on exercise capacity and quality of life (QoL) for CHF patients, we conducted a systematic review and meta-analysis of 33 randomized controlled trial (RCTs) involving 2,465 patients with CHF (**Paper I**). **Paper II** is a descriptive study which evaluates *Baduanj*in intensity and cardiopulmonary responses during practice. Participants were examined during two separate sessions to measure their maximum exercise capacities, as well as their cardiopulmonary responses during *Baduanjin* practice. We compared the measurements obtained during *Baduanjin* with their maximum exercise capacities. **Paper III** is a pilot RCT evaluating the feasibility of the BESMILE-HF program. We recruited eighteen patients with CHF: 8 in a BESMILE-HF group and 10 in a control group. Participants in both groups received the usual medications, with the intervention group also receiving the BESMILE-HF program for 6 weeks. We explored feasibility using participants' involvement in the intended intervention. Clinical outcome assessments were conducted at baseline and post-intervention, while adverse events were captured throughout the study period. **Paper IV** is a qualitative study nested in the pilot RCT to explore the experience of practicing *Baduanjin*. After the pilot RCT ended, seven participants in the intervention groups agreed to participate in the semi-structured interview. All questions were open-ended, and follow-up questions provided a deeper understanding of areas that appear essential for each individual.

Results: Based on moderate-level evidence, adding TCEs into routine pharmacotherapies was associated with statistically significant improvements in exercise capacity and QoL. When compared to general exercise, we found superior improvements in the TCEs group; these were significant for QoL, but not for exercise capacity. We also found evidence that TCE is safe, and that there is high adherence to TCEs programs (**Paper I**). In terms of *Baduanjin*'s intensity, both measures of relative intensity measured in this study, $\%VO_{2max}$ and $\%HR_{max}$, categorize *Baduanjin* as a moderate-intensity exercise. This makes it suitable for improving CHF patients' exercise capacity (**Paper II**). In addition, both the VO_2 and the HR responses exhibited a bimodal pattern during the exercise session. Further, the average energy expenditure was estimated as 23.3 kcal for a 9-mintue *Baduanjin* session. In **Paper III,** we found that the

BESMILE-HF program was well received by patients. As a home-based EBCR program, the intervention group demonstrated good compliance with the required exercises. We also found that one's initial self-efficacy had a positive effect on the total exercise time. More importantly, intervention can improve participants' exercise self-efficacy and may have benefit on exercise capacity. Interviews (**Paper IV**) demonstrated that *Baduanjin* is perceived as being easy for participants to learn. However, the coordination of the mind, the movements, and the breathing in *Baduanjin* exercise can only be achieved progressively through repeated practice. They also perceived that regular high-quality *Baduanjin* practice provides many benefits for both the mental and the physical health. Moreover, the perceived training benefits played a crucial role in adherence to home-based training.

Conclusion: TCEs may represent a promising rehabilitation therapy as an adjunctive to routine pharmacotherapies, or as an alternative to conventional exercise for patients with CHF. *Baduanjin*'s eight simple postures are not only accessible and learner-friendly, but also suitable for CHF, as it is a moderate-intensity aerobic exercise without excessive cardiopulmonary stress. When practicing *Baduanjin*, it is essential for the practitioner to coordinate the mind, movements and breathing in *Baduanjin* exercise, alongside ongoing correct execution. Practicing *Baduanjin* may promote the overall physical and psychological health of CHF patients. Moreover, integrating *Baduanjin* into cardiac rehabilitation programs may increase patients' long-term adherence to exercise by improving exercise self-efficacy. A larger sample size and a longer follow-up period are needed to confirm its benefit on clinical outcomes.

Keywords: Chronic heart failure, exercise-based cardiac rehabilitation, *Baduanjin*, tradition Chinese exercise, exercise capacity, quality of life, cardiopulmonary exercise test, self-efficacy

LIST OF SCIENTIFIC PAPERS

I. **Chen X**, Savarese G, Cai Y, Ma L, Stålsby Lundborg C, Jiang W, Wen Z, Lu W, Marrone G.
Taichi and Qigong Practices for Chronic Heart Failure: A Systematic Review and Meta-analysis of Randomized Controlled Trials
Evidence-Based Complementary and Alternative Medicine. 2020 :2034625

II. **Chen X**, Marrone G, Olson TP, Stålsby Lundborg C, Zhu H, Wen Z, Lu W, Jiang W.
Intensity Level and Cardiorespiratory Responses to Baduanjin Exercise in Patients with Chronic Heart Failure
ESC Heart Failure, 2020;7(6):3782-91

III. **Chen X**, Jiang W, Olson TP, Stålsby Lundborg C, Wen Z, Lu W, Marrone G.
F**easibility and preliminary effects of the BESMILE-HF Program on Heart Failure Patients: a Pilot Randomized Controlled Trial**
Submitted

IV. **Chen X**, Salazar M, Jiang W, Huiying Zhu, Marrone G, Wen Z, Lu W, Stålsby Lundborg C
Traditional Baduanjin Exercise Through the Eyes of Patients with Chronic Heart Failure: A Qualitative Content Analysis Study
Manuscript

ADDITIONAL PAPERS REFERENCED IN THE THESIS

I. **Chen X**, Jiang W, Lin X, Stålsby Lundborg C, Wen Z, Lu W, Marrone G.
Effect of an exercise-based cardiac rehabilitation program "Baduanjin Eight-Silken-Movements with self-efficacy building" for heart failure (BESMILE-HF study): study protocol for a randomized controlled trial
Trials. 2018;19(1):150.

CONTENTS

LIST OF ABBREVIATIONS

6MWD	6-minute walking distance
BESMILE-HF	Baduanjin Eight-Silken-Movement wIth SeLf-Efficacy building for Heart Failure
BNP	B-type natriuretic peptide
CHF	Chronic heart failure
CIs	Confidence intervals
CPX	Cardiopulmonary exercise testing
CVDs	Cardiovascular diseases
EBCR	Exercise-based cardiac rehabilitation
GPHCM	Guangdong Provincial Hospital of Chinese Medicine
HADS	Hospital Anxiety and Depression Scale
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Heart rate
IQR	Interquartile range
LMICs	Low- and middle-income countries
LVEF	Left ventricular ejection fraction
MET	Metabolic equivalent
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NT-proBNP	N-terminal B-type natriuretic peptide
NYHA	New York Heart Association
QoL	Quality of life
RCTs	Randomized controlled trial
SD	Standard deviation
TCEs	Traditional Chinese Exercises
VO_2	Oxygen consumption
VO_{2peak}	Peak oxygen consumption

1 INTRODUCTION

A hallmark symptom of chronic heart failure (CHF) is impaired exercise tolerance and poor quality of life (QoL). Scientific evidence has shown that exercise-based cardiac rehabilitation (EBCR) therapy improves exercise capacity and QoL in these patients [1, 2]. However, the sub-optimal use of EBCR remains troubling and warrants high priority in global healthcare [3].

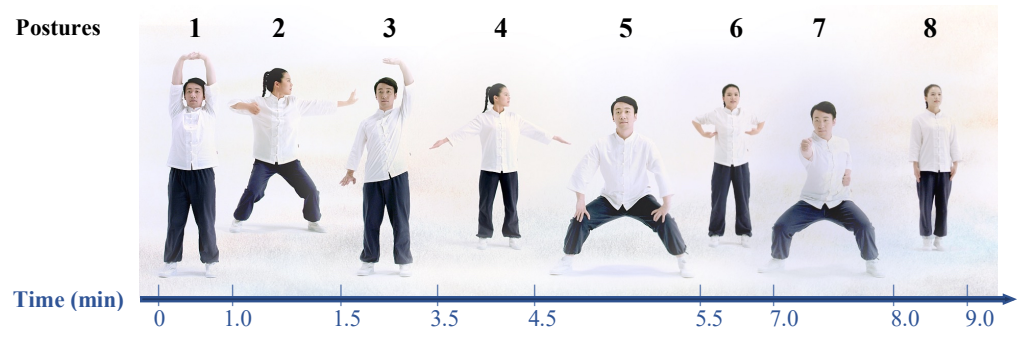
While many countries have reported gaps in CHF patient referrals to existing EBCR programs, China has faced an even greater 'upstream' challenge—a lack of available EBCR programs [4]. A national survey showed that only 24% of China's tertiary hospitals have EBCR programs [5]. Unfortunately, the type of comprehensive EBCR programs delivered in high income countries are not feasible in China due to the dearth of rehabilitation facilities, trained professionals, as well as unaffordability [5].

One possible solution tailored to the Chinese setting is a traditional *Baduanjin* exercise which is usually practiced at home. *Baduanjin*, translated as Eight Silken Movements, is a form of ancient martial arts that originated in China and has been culturally accepted as being beneficial to one's health in Chinese society [6]. This practice has evolved based on traditional Chinese medicine theory and is characterized by interplay between flowing circular physical postures and movements, mindfulness, and breathing exercise in harmony [7]. *Baduanjin* is easy to learn and has minimal physical and cognitive demands because it entails only eight simple movements (**Figure 1**).

A novel and contextually adapted EBCR program using *Baduanjin*, BESMILE-HF, has been developed at the Guangdong Provincial Hospital of Chinese Medicine (GPHCM)—a tertiary care hospital and one of the oldest and largest Chinese medicine hospital groups in China [8]. **BESMILE-HF** is an acronym for the **B**aduanjin **E**ight-**S**ilken-**M**ovement w**I**th Se**L**f-**E**fficacy building for **H**eart **F**ailure. In this program, *Baduanjin* has been applied as the core constituent in multi-component EBCR including evaluation, consultancy, and education, as well as a series of self-efficacy building strategies to increase adherence, and to maintain exercise compliance over time.

This thesis includes a systematic review of current evidence on traditional Chinese exercises (TCEs) for CHF, a cross-sectional study to confirm *Baduanjin* intensity, a pilot randomized controlled trial to evaluate the BESMILE-HF program's feasibility, and a qualitative study to explore participants' experience in the BESMILE-HF program.

Figure 1 A 9-minute Baduanjin exercise training session, including eight postures, involved muscle groups, and their corresponding durations (Paper II) [9]



	Name of postures and involved muscle groups	Duration
1	**Holding the hands high with palms up to regulate the internal organs** Muscles: Chest (Pectorals), Back (Latissimus Dorsi, Trapezius), Abs (External Obliques, Rectus Abdominis), Shoulders (Deltoids), Arms (Biceps, Triceps), Forearms	**60 secs**
2	**Posing as an archer shooting both left- and right- handed** Muscles: Gluteals, Quadriceps, Hamstrings, Calves (Gastrocnemius, Soleus), Chest (Pectorals), Back (Latissimus Dorsi)、Sternocleidomastoid, Shoulders (Deltoids), Arms (Biceps, Triceps), Forearms	**90 secs**
3	**Holding one arm aloft to regulate the functions of the spleen and stomach** Muscles: Chest (Pectorals), Back (Latissimus Dorsi, Trapezius), Abs (Obliques, Rectus Abdominis), Shoulders (Deltoids), Arms (Biceps, Triceps), Forearms	**60 secs**
4	**Looking backwards to prevent sickness and strain** Muscles: Sternocleidomastoid, Shoulders (Deltoids), Chest (Pectorals), Back (Latissimus Dorsi), Abs (Rectus Abdominis, External Obliques, Internal Obliques, Transversus Abdominis)	**60 secs**
5	**Swinging the head while lowering the body to relieve stress** Muscles: Gluteals, Quadriceps, Hamstrings, Calves (Gastrocnemius, Soleus), Back (Latissimus Dorsi, Trapezius, Erector Spinae), Abs (Rectus Abdominis, External Obliques, Transversus Abdominis)	**60 secs**
6	**Moving the hands down the back-legs-feet to strengthen the kidneys** Muscles: Shoulders (Deltoids), Chest (Pectorals), Back (Latissimus Dorsi, Trapezius, Erector Spinae), Gluteals, Hamstrings, Calves (Gastrocnemius, Soleus)	**90 secs**
7	**Thrusting the fists and glaring the eyes to enhance strength** Muscles: Gluteals, Quadriceps, Hamstrings, Calves (Gastrocnemius, Soleus), Sternocleidomastoid, Shoulders (Deltoids), Back(Trapezius), Arms(Biceps, Triceps), Forearms	**60 secs**
8	**Raising and lowering the heels to cure disease** Muscles: Back (Erector Spinae), Gluteals, Hamstrings, Calves (Gastrocnemius, Soleus)	**60 secs**

2 BACKGROUND

2.1 HEART FAILURE

2.1.1 Burdens, clinical manifestations, phenotypes

Cardiovascular diseases (CVDs) are the leading causes of disability and death in the world and heart failure (HF) is the common end pathway of many CVDs [10]. HF is a clinical syndrome characterized by shortness of breath, reduced exercise capacity, fatigue, and periphery edema, induced by left (or global) ventricular dysfunction, often with signs of congestion [11]. Earlier definitions of HF classified the syndrome as a diastolic or systolic dysfunction, however, for most patients, abnormalities of systolic and diastolic function coexist. The current definition of heart failure is based on the left ventricular ejection fraction (LVEF). HF is subcategorized into three groups: heart failure with reduced ejection fraction (HFrEF) if the EF is <40%, heart failure with mid-range ejection fraction (HFmrEF) when the EF is 40-49% and heart failure with preserved ejection fraction (HFpEF) when the EF is ⩾50%.

HF occurs in approximately 1-2% of the adult population in high income countries [12]. It carries a poor prognosis; observational data from Europe [13] have shown that one-year all-cause mortality for patients with acute heart failure is 17%, and for stable or ambulatory it is 7%. The International Congestive Heart Failure Study representing Africa, China, India, the Middle East, Southeast Asia, and South America, reported an overall 1-year mortality of 16.5%, with substantial variation by region (15% in Southeast Asia, 34% in Africa, 23% in India, 9% in South America, 9% in the Middle East, and 7% in China) [14].

The prevalence of HF is expected to continue to increase due to the aging population, increasing prevalence of risk factors, and improved post-myocardial infarction survival. Mortality rates for HF are high even for patients compliant with best available treatments [15].

2.1.2 Exercise intolerance and measurements

Exercise intolerance is a primary symptom among patients with CHF, and is a strong determinant of prognosis, and of reduced QoL [16]. Exercise intolerance is defined as “an impairment in the capacity to perform physical activities accompanied by symptoms of significant dyspnea and/or fatigue” [17]. The pathophysiological mechanisms of exercise intolerance in HF are multifactorial. These include impairments in cardiac and pulmonary reserve, as well as reduced respiratory and peripheral skeletal muscle perfusion and/or function, which contribute to the overall syndrome to varying degrees.

Several methods have been proposed to clinically estimate or directly assess exercise capacity [18]. A summary of their comparative performance is listed in **Table1**. The New York Heart Association (NYHA) functional classification is the most commonly used subjective method (**Appendix 1**). Although it has advantage of low expense and ease-of-use, there are several limitations: 1) limited discriminatory power and reproducibility especially between NYHA

functional classes II and III; 2) low sensitivity to changes over time; and most importantly, 3) the inability to define mechanisms of exertional intolerance [18].

Objective quantitative methods for the assessment of functional and/or exercise capacity include the 6-min walk distance (6MWD), graded exercise testing with electrocardiography (ECG), and cardiopulmonary exercise testing (CPX) [18]. Nowadays, CPX is the accepted gold-standard assessment tool for exercise capacity [19]. It allows for a refined, noninvasive assessment of the multiple mechanisms which limit the exercise capacity of patients with HF. However, compared with other exercise tests, CPX is more expensive, more time-consuming, and requires specialized personnel and equipment [18].

Table 1 Pros and cons of different methods used to quantify exercise intolerance in HF patients (adapted from *Del Buono et al 2019* [18])

Modality	Pros	Cons
NYHA	Easy and quick to perform, cost-free, high prognostic value	Lack of reproducibility, low discriminatory power, no data for EI mechanisms
ECG stress testing	Easy to perform, negligible costs, detects CI	Inaccurate exercise capacity estimates, incomplete understanding of EI due to lack of expired gas analysis/submaximal effort
6MWD	Simplicity, feasibility, negligible costs, prognostic value of the distance covered and changing overtime	Submaximal effort, no data for EI mechanisms
CPX	Provides insight into understanding the mechanism of exercise intolerance, reproducibility, high prognostic value, monitoring of therapeutic response, detection of CI, quantification of patient effort; it can be paired with cardiac imaging or invasive monitoring	Time-consuming, expensive, specialized personnel required, complexity

*6MWD=6-min walk distacne; CI=chronotropic incompetence; CPX=cardiopulmonary exercise testing; ECG=electrocardiography; EI=exercise intolerance; HF=heart failure; NYHA=New York Heart Association.

2.1.3 Health related quality of life and measurements

Multiple studies have demonstrated that HF has a negative effect on patients' physical, social, psychological, and emotional well-being [11]. Patients with HF often experience difficulty in performing daily activities, and suffer economic, sexual, and psychosocial problems. These difficulties ultimately impair patients' health-related QoL, which may be as important as survival to patients living with HF. Furthermore, studies have consistently demonstrated that poorer QoL is correlated with increased hospitalization and death [11].

The change in QoL is usually measured before and after treatment to estimate the perception of QoL, disease frequency and severity. Treatment effects important for QoL are measured using two types of clinical instruments. The first category contains generic instruments like Short-Form 36, and Euro quality of life 5 dimensions (EQ-5D), which are multidimensional and attempt to measure the core dimensions of QoL. However, they fail to capture smaller disease-specific effects and do not always respond to changes in specific conditions. The second category of instruments are those focused on the disease-specific effects of HF. Examples include the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire. These are perceived as more relevant than generic measures due to the use of an individual's symptoms in order to derive an understanding of their experiences living with the disease.

2.2 EXERCISE-BASED CARDIAC REHABILITATION

2.2.1 Scope, clinical evidence and guideline recommendations

CHF is a life-threatening condition requiring a life-long secondary prevention strategy to decrease morbidity and mortality, as well as to improve QoL. Although CHF was once considered a contraindication to exercise, numerous studies demonstrate that regular exercise is safe and associated with a multitude of benefits in appropriately selected CHF patients [1, 20-23]. Over the last several decades, exercise has become the cornerstone of a comprehensive "secondary prevention" strategy in cardiac rehabilitation. Secondary prevention strategies also address risk factors, nutrition, psychological, behavioral and social factors that can affect patient outcomes [24]. Therefore, exercise-based cardiac rehabilitation (EBCR) programs have become an integral part of the standard of care in modern cardiology [25].

It has been demonstrated that EBCR yields a range of benefits for CHF patients. These include improvements in exercise capacity, left ventricular hemodynamics, QoL, a decreased risk of hospitalization and death, as well as improvements in psychological status and function [26]. Based on current evidence on clinical outcomes and costs, international guidelines on the management of CHF, including those of the ACC/AHA and ESC, consistently recommend EBCR or exercise as an effective and safe intervention. In the 2020 ESC Sports Guidelines, the preferred activity for patients with CHF is a 20-60 min training on 3-5 days a week with intensity equal to 40-80% of VO_{2max} with ideally progressing intensity over the rehabilitation time [27].

2.2.2 Underutilization

Despite both the presence of clinical practice guideline recommendations to refer cardiac CHF patients to rehabilitation and the clear benefits, EBCR programs are grossly under-used. Worldwide, there is a low availability of EBCR: only 38.8% of countries globally have EBCR programs [3]. Specifically, 68% of high-income and 23% of low- and middle-income countries (LMICs) have EBCR programs [3]. This demonstrates that EBCR availability is much lower than that of other evidence-based secondary prevention therapies, such as revascularization and pharmacological therapies. In high-income countries, physician referral to EBCR has been highlighted as a key barrier in several studies with 33%–71% of eligible CHF patients not referred, and hence unable to access EBCR programs [28-31]. In LMICs, a recent study reported a high degree of variability in EBCR referral rates ranging from 5% to 90%, with the majority of countries referring <40% of eligible patients. Attendance rates post referral were also suboptimal and displayed a high level of geographic variation [32].

2.3 THE CHINESE PERSPECTIVE

2.3.1 Heart failure epidemiology

Studies on incidence of HF in China are rare and the prevalence is similar to Western countries, 1-2% [33]. The only national survey in 2003 reported that the prevalence of HF in China was 0.9% [34]. This study suggests that there were more than 4 million HF patients in China – an estimate some experts predict has doubled since the study [35]. The China HF Registry Study (China-HF) reported an in-hospital HF mortality rate of 5.3% between 2012 and 2014 [36], similar to the 2000 rate [37]. There are few large-scale studies on the long-term prognosis of HF patients after discharge, and only limited data are available from single centers. A report, representing North China, from the Peking Union Medical College Hospital showed that the 1-, 2-, and 3-year mortality rates of 187 HF patients during 2007 and 2009 were 14%, 22%, and 32%, respectively [38]. Other data, representing East China, from 164 HF patients treated in Zhongshan Hospital, Fudan University between 2009 and 2010 suggested that the all-cause mortality was 21% after a 2.4-year follow-up [39].

China's economy, social and natural environment, standard of living, and medical and public health conditions have undergone myriad changes in recent decades, resulting in a significant change in the spectrum of HF causes [35]. Studies suggested that the primary etiology of HF in China has transformed from rheumatic heart disease to coronary heart diseases during the last 30 years of the 20th century [40, 41]. In general, coronary heart disease, hypertension, and rheumatic heart disease are currently the primary causes of HF in China [42].

2.3.2 Socio-demographics, clinical characteristics, and disease burdens

In 2016, a cross-sectional survey involving 933 HF patients (the Adelphi HF Disease Specific Programme (DSP) study) explored the burden of disease among Chinese HF patients [43]. This study is the most recent and largest nation-wide survey that provides information specific to Chinese HF patients.

The DSP study provided data on the socio-demographics and clinical characteristics of Chinese HF patients. In this study, 55% of the patients were male, the mean age was 66 years and 80% of participants were retired. Patients had a mean body mass index of 24 kg/m^2, 10% were smokers at the time of the study, and 7% were consumers of alcohol at the time of the study. On average, patients had been diagnosed with HF for 577 (SD: 795) days. The proportions of patients with HFrEF and HFpEF were 51% and 37%, respectively; and the proportions of patients with NYHA I, II, III, IV were 23%, 48%, 25%, and 4%, respectively. The DSP study demonstrated a high disease burden in HF patients: the majority of patients reported moderate or extreme pain or discomfort that affected their health status. HF also disrupted patients' daily lives: only 21% reported that "they were always able to leave the house; and 29% reported that "they were rarely or never able to leave the house due to HF". QoL and psychological status among study participants was lower than that observed among the general elderly population (defined as either >60 or >65 years of age) in China [44, 45].

The DSP study also was the first to detail the economic costs HF incurs on patients. In line with universal health insurance coverage in China which exceeded 95% of the population in 2011 [46], all but a few HF patients included in this study were enrolled in an insurance plan. Most patients were enrolled in a plan that covered at least part of their HF-related drug costs. However, 24% of patients had an insurance plan covering their full cost of treatment; 51% of patients paid a fixed amount for their treatment, while 31% paid a fixed percentage.

2.3.3 Current status of cardiac rehabilitation in China

Given the burden of CVD in China, especially the burden of HF, secondary prevention strategies through EBCR are vital to stemming this growing epidemic. However, EBCR remains under-utilized in clinical practice. Efforts to improve the suboptimal use of EBCR require an understanding of the current status of this service's implementation, as well as a careful analysis of barriers specific to the Chinese setting.

2.3.3.1 Availability

While many countries across the world report gaps in the referral of eligible patients to existing EBCR programs [47, 48], studies suggest an even greater 'upstream' challenge throughout China—a lack of available EBCR programs or services to which eligible patients could potentially be referred; for example, only 24% of the tertiary hospitals have EBCR services [5]. Cardiac rehabilitation remains a novel concept in Mainland China, receiving scant attention until recent years. In the mid-1980s and early 1990s, more and more hospitals in China began offering EBCR programs [4]. Currently, hospitals with EBCR programs are dispersed throughout 20 provinces [4] and the number of cardiac rehabilitation centers increased from only 30 in 2012 to 200 in 2016. However, this promising figure is dwarfed by the immense CVD burden in China.

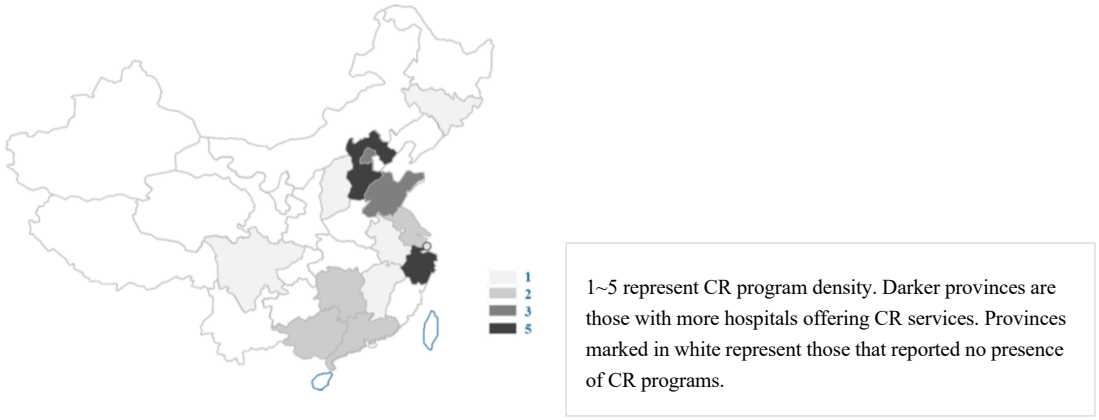


Figure 2. Geographic distribution of the number of cardiac rehabilitation programs reported in hospitals in China, by province [5]

2.3.3.2 Cost

In contrast to many high-income countries where EBCR service is embedded in the health care insurance systems, EBCR service relies on out-of-pocket payment systems in China because National Health Service does not pay for a patient's participation in a EBCR program after hospital discharge. This further leads to a financial burden for most patients.

For example, at Guangdong Provincial Hospital of Chinese Medicine, the average cost for one EBCR session including exercise training is around RMB 100/US$15. This means that patients need to pay a mean out-of-pocket fee of RMB 3600/US$540 for a standardized 36-session EBCR program which usually lasts for three months. The monthly EBCR-related costs (RMB 1200/US$180) are 4 times higher than the average monthly general treatment-related costs (RMB 300) [33]. Moreover, in the context of the minimum monthly wage in China, which varied from ¥1,150 (US$193) to RMB 2,480/US$382 in 2020 [49], the EBCR-related costs are considerable and likely to cause additional consternation to those patients who are not in a comfortable financial situation.

2.3.3.3 Clinical Guidelines and Consensus

In 2015, the Committee of Cardiac Rehabilitation and Prevention at the Chinese Association of Rehabilitation Medicine published Chinese guidelines for rehabilitation/secondary prevention of cardiovascular diseases. This was a milestone in the development of EBCR; it was updated in 2018 [50]. Disease-specific EBCR guidelines are also available. For example, in 2014, the first Chinese expert's consensus on exercise rehabilitation for CHF (hereinafter referred to as "the Consensus") was published [51]. It was updated in 2020 [52]. The consensus provides details to help doctors evaluate CHF patients, prescribe exercise, judge effectiveness and implement exercise programs.

2.3.3.4 Practice patterns

EBCR practice patterns remain rudimentary and unstandardized. For example, in the vast majority of cases, cardiac rehabilitation comes in the form of verbal information supplemented

by leaflets and booklets emphasizing early mobilization and identification and control of risk factors. Most programs are coordinated by a nurse, with few using other healthcare professionals such as exercise physiologists, dieticians or physiotherapists, as is recommended in the current guidelines [50]. One exception is tertiary hospitals, in which components of the EBCR programs are similar to those reported in other countries [5].

2.3.3.5 Referral rates

Data regarding EBCR referral rates in China is lacking. Currently, there is no cardiac rehabilitation referral system in China; and few cardiologists add EBCR into their daily clinical practice for their patients [5]. Physicians, in both high and middle-income settings, have been found to play an important role in EBCR utilization [3, 32, 53]. In China, infrequent physician referrals may be compounded by the lack of hospital staff with training in EBCR. At present, there are only 15 certificated EBCR training organizations in China and EBCR is not part of the routine training for cardiologists [50]. This results in inadequate understanding of EBCR's benefits and inadequate assessment of a patient's (in)ability to participate [5]. Furthermore, compensation for physicians for providing EBCR is lower than that for interventional cardiologists. This likely influences physician choice of specialty and area of practice [50].

2.3.3.6 Barriers

A study has reported that among eligible patients with coronary heart disease who were offered a standard EBCR program, only 14.3% opted to do EBCR [54]. There is a paucity of studies on patient-related barriers to EBCR in China, and there are no studies specific to CHF patients. One study, conducted in Nanjing, has investigated the barriers in seeking EBCR among patients with coronary heart disease. It found that the most common reason for failure to do EBCR was unaffordability. This may be attributed to perceived insufficient healthcare resources and an under-developed reimbursement system [54]. Other studies have reported the following patient-related EBCR barriers: lack of awareness, motivation, interest [5, 55], female sex, old age, low socioeconomic status [54], time, transportation [4], disease-related symptoms and comorbidities [43].

2.4 CONTEXTUALLY ADAPTED EBCR IN CHINA

In China, solutions for improving EBCR utilization among HF patients must be tailored to the barriers caused by resource scarcity, especially the national health system's finances. In addition, resource-adapted EBCR programs must be sensitive to the aforementioned patient- and physician-related barriers, as well as the cultural contexts in which they are embedded.

2.4.1 Low-cost exercises

The practicalities and realities of providing a comprehensive EBCR program require clever usage of available low-cost exercises [56]. Among those available low-cost exercises, research interest initially pointed towards the easiest daily activity, walking. In addition to walking, many studies in China have shown that other outdoor activities such as biking, running, and swimming improve cardiac function and QoL in CHF patients. Chinese square dancing is an

aerobic exercise that many elderly Chinese citizens perform to maintain fitness in public spaces. It is a simple, free, and easy-to-learn style of dancing pattern that allows for sustained physical activity.

2.4.2 Home-based exercise

Home-based exercise training is effective as center-based exercise training for cardiac rehabilitation in patients with HF [48]. In 2018, a randomized controlled study evaluated the effects of an 8-week home-based telehealth exercise training program, including 32 exercise training sessions with regular telephone or instant messaging follow-ups and consultations, on patients with HF [57]. Significant improvements were found in QoL and 6MWD; and these benefits were sustained for 4 months after the post-test. The study's attrition rates were low (14.3%) compared to previously reported attrition rates (30%-70%) in center-based exercise training trials [26]. Another study, of patients with myocardial infarction in Xi'an, China, found that a home-based EBCR program including education and a home exercise plan in combination with various adherence strategies, improved QoL and reduced anxiety in comparison with usual care [58].

2.4.3 Traditional Chinese Exercises

Unlike conventional exercise modalities which focus on strengthening the physical body, TCEs aim for harmonious flow of energy (*qi*) in the body [59]. This is attained using slow movements synchronized with meditation and regulated breathing. TCEs are a form of ancient martial arts that originated in China and is culturally accepted as being beneficial to one's health, especially with regard to its ability to fight disease. Nowadays, the Chinese government is promoting TCEs across the country to improve health maintenance ("Healthy China 2030" strategy) [60]. It is an adaptable form of daily exercise that can be practiced any place and any time. It requires no special equipment or significant time investment. Therefore, TCE has the potential to become an integral part of EBCR programs to increase EBCR uptake in China.

2.4.4 BA-DUAN-JIN

Baduanjin, variously translated as Eight Pieces of Brocade, Eight-Section Brocade, Eight Silken Movements or Eight Silk Weaving, is a form of TCE established over 1,000 years ago [6]. It is characterized by interplay between flowing circular physical postures, the mind, and breathing exercises conducted in harmony. *Baduanjin* is easy to learn with minimal physical and cognitive demands because it only contains eight simple movements. *Baduanjin* consists of sitting and standing forms [6], and the newest version of the latter was stipulated by the General Administration of Sport of China [61]. It has been standardized as a set of eight sequential movements for the limbs, body-trunk and eyes (**Figure 1**) [59].

2.4.4.1 How does Baduanjin fit for heart failure?

Baduanjin is a multicomponent intervention that integrates a number of training elements that are relevant to the treatment of patients with heart failure. Key elements included in *Baduanjin*

exercise are: 1) physical exercise, 2) respiratory muscle training and breathing techniques, and 3) mindful-based training.

Although the greatest importance should be attached to aerobic exercise, other training modalities such as stretching, flexibility training, upper-/lower-extremity exercises are also considered to be supplementary to combat exercise intolerance in HF [62]. *Baduanjin* provides a mixture of all these recommended training modalities via the use of a set of 8 postures. Posture 8 emphasizes a high-impact and weight-bearing movements, is a form of lower extremity training; postures 2,5,7 employ a horse-riding stance which specifically target the quadriceps [63]; postures 1, 2, 3, and 7 require rotating, raising, or stretching the forearms； as well as clenching or punching fist, these provide physical conditioning of the upper extremities [64]; and postures 4 and 6, require twisting the body and head to enhance stretching or flexibility[65]. Moreover, previous studies have confirmed beneficial effects of *Baduanjin* on handgrip strength; trunk and hip flexibility; lower extremity power, lower limb proprioception function; physical balance and flexibility; and aerobic ability measured by 6MWD [66, 67].

In HF, respiratory muscle weakness and inefficiency contributes to breathlessness, exercise impairment, low QoL, and poor prognosis [68], which make the addition of respiratory muscle training advantageous in cardiac rehabilitation. *Baduanjin* includes elements of respiratory muscle and breathing training that aim to increase muscle strength and endurance, decrease mechanical loads such as chest wall resistance, and deepen and reduce the respiratory rate. Results of a meta-analysis showed that *Baduanjin* significantly improved respiratory efficiency (vital capacity) [67].

The pathological role of stress and increased sympathetic activity in the development and progression of HF is well established [11, 69, 70]. Mindfulness-based interventions includes meditative exercises using focused breathing as a tool, these have been effective in reducing stress, anxiety and depressive symptoms [71] as well as improving physical functioning [72, 73] and signs of decreased cardiovascular sympathetic activity [72, 73]. Hence, patients with HF might benefit from mindfulness-based intervention. A fundamental component of *Baduanjin* is mindfulness-based training by focusing attention on bodily sensation, movement, breath, and emotion, which fosters acute self-awareness, both physically and emotionally. Previous studies, in non-HF patients, have reported that *Baduanjin* is beneficial for mental health; sympathetic/parasympathetic balance; alleviating daily fatigue; improving sleep quality; status of depression and anxiety; and QoL [66, 67].

2.4.4.2 Baduanjin, exercise capacity, and QoL

The rapidly increasing number of practitioners in *Baduanjin* around the world has attracted considerable attention from the research community to investigate effects on a variety of health-related outcomes in both healthy and clinical populations [74]. More specifically, the healthy populations were college students, older adults, and middle-aged men and women [66, 67, 75-79]. Despite the growing interest, there is still a scarcity of scientific studies on its value for CHF patients and only six randomized controlled trial (RCTs) are available on this topic

[80-85]. Furthermore, the study design and training protocols from different *Baduanjin* studies vary significantly, making the results difficult to compare.

The most well-designed and well-conducted RCT in terms of the current reporting guidelines, published in English, is a study conducted in Taiwan [84]. In this study, Chen et al conducted a multi-center RCT to evaluate the effects of *Baduanjin* exercise on fatigue and QoL in HF patients in Taiwan. Patients in the intervention group (n=39) underwent a 12-week *Baduanjin* exercise program, which included *Baduanji*n exercise three times per week for 12 weeks at home. The control group (n=41) received usual care and received no intervention. Compared to the control group, the *Baduanjin* group demonstrated a significantly greater improvement in fatigue and QoL from baseline to week 12 after the intervention.

The other five RCTs were conducted in mainland China. In Xiong et al (2016) study [80] , the intervention group self-practiced Baduanjin, 30 minutes per day and 5 times a week for 12 weeks, as an adjunctive to usual care (n=33); and the control group received only usual care (n=30). Compared to controls, significant improvements were observed in LVEF, 6MWD, QoL, cognitive function, daily living ability, and rates of re-hospitalization after 12 weeks. The improvements in 6MWD and QoL were also confirmed in the RCT conducted by Li et al (2016), however, this RCT used walking as comparator [85]. The rest three RCTs shared a similar design [81-83], but HF patients were included during hospitalization. Patients were randomized to the intervention group, learning how to practice *Baduanjin* before discharge, or the control group. All patients were followed-up for 1 year and outcome assessments were conducted at the time of discharge and after 1 year. Compared to the control group, three RCTs reported significant improvements in 6MWD [81-83]; and two studies reported significant reduction in the number of one-year re-hospitalization [81, 83].

Concerning these five studies, one of the most consistent finding was the significant improvement in the 6MWD, especially immediately after intervention [80, 85], which indicates that *Baduanjin* has beneficial effects on exercise capacity. However, they all applied a single-center design and these five RCTs haven’t provided complete descriptions of the delivery process, limiting theor ability to interpret findings into clinical application.

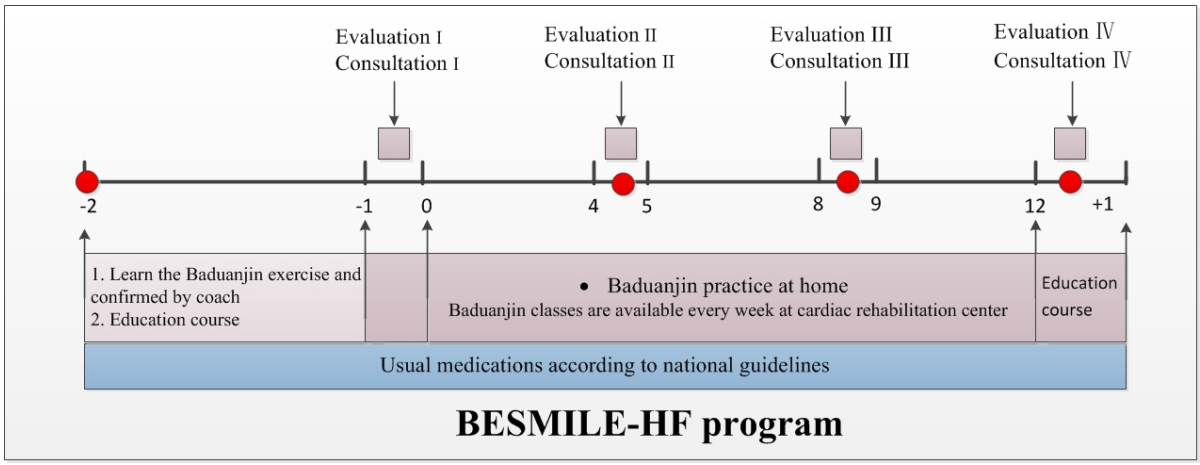
2.4.5 Optimizing adherence with exercise training

Structured exercise programs are not sufficient on their own; interventions must also include adherence strategies to increase and maintain exercise over time [86]. Self-efficacy is reported to be the most dominant factor in the uptake and maintenance of exercise among the CHF population [87]. Study results support the incorporation of adherence strategies designed to foster exercise self-efficacy [86]. Self-efficacy is a psychological construct based on social cognitive theory and it describes the interaction between behavioral, personal, and environmental factors in health and chronic disease. The theory of self-efficacy proposes that the confidence in one's capability to perform certain health behaviors influences a patient's engagement in and performance of those behaviors, which in turn influences health outcomes.

2.4.6 BESMILE-HF program

A novel and contextually adapted EBCR program using *Baduanjin*, BESMILE-HF, has recently been developed at GPHCM. **BESMILE-HF** is an acronym for the **B**aduanjin **E**ight-**S**ilken-**M**ovement w**I**th Se**L**f-**E**fficacy building for **H**eart **F**ailure. In this program, *Baduanjin* has been applied as the core constituent in a multi-component EBCR including evaluation, consultancy, and education, as well as a series of self-efficacy building strategies to increase adherence, and to maintain exercise compliance over time (**Figure 3**).

Figure 3 Procedures of the BESMILE-HF program



2.4.6.1 Pre-phase of BESMILE-HF program: 2 weeks before the start of exercise

Baduanjin learning class:

- we will employ two professional coaches who have engaged in teaching Baduanjin exercise for over five years to teach and guide participants' training;
- patients are required to learn how to practice until they master the exercise, which will be confirmed by the professional coaches.

Education course which will cover to following topics:

- basic knowledge of chronic heart failure, and
- basic knowledge of exercise-based cardiac rehabilitation.

An initial evaluation of patients' exercise capacity (-1 week to 0 week):

- evaluation is conducted by cardiologists and physiotherapist;
- evaluation is based on reviewing medical history, cardiopulmonary exercise test's results, and performance of Baduanjin exercise (recording heart rate and oxygen consumption during their practice);
- evaluation results will guide the goal setting process during consultation

An initial consultation lasting 20–30 minutes will be conducted by cardiologists and nurses (-1 week to 0 week):

- development of exercise prescription: cardiologists and nurses will work collaboratively with patients to set goals, which is guided by the initial evaluation and rules as following:
- in general, the recommended exercise volume is to practice Baduanjin for 30 minutes per day, five days per week with a total of 150 minutes per week [62, 88];
- patients should be encouraged to progressively increase exercise duration, as tolerated, until they will be able to tolerate one bout of 30 minutes [89];
- patients with a baseline exercise capacity < 3 METs should be encouraged to start with the sitting-form Baduanjin and patients with exercise capacity > 3 METs can start with standing-form Baduanjin [90].
- medications management, recognition and problem-solving of symptoms and signs during exercise.

2.4.6.2 Exercise phase of BESMILE-HF program: a 12-week period of intervention

Baduanjin exercise:

- home exercise: participants will be encouraged to practice Baduanjin at home with the instruction of picture-based brochure;
- alternatively, for those who would like to practice in class, participants will be able to attend the coach-guided class held at the rehabilitation center after making appointments with the research assistants. In the class, professional coaches will demonstrate exercise techniques, evaluate the participants' performance, and give feedback to the participants.
- Baduanjin classes will be available at a variety of times, including weekdays, weekends, and evening sessions throughout the study period.
- exercise logs are designed to record each session of exercise daily, including duration in minutes and frequency.

Three evaluations at 4^{th}, 8^{th} and 12^{th} week:

- re-assessment of exercise capacity and performance of Baduanjin exercise;
- clinical conditions and relevant physical examinations
- Three consultations at 4th, 8th and 12th week:
- difficulties in goal accomplishment and revision of exercise prescription;
- medications management, recognition and problem-solving of symptoms and signs during exercise.

Patients will be required to attend education courses at 12^{th} wee:

- long-term maintenance of exercise; and
- disease management in daily life.

3 AIMS

The overall aim was to provide knowledge, experience, and evidence on how to effectively deliver a contextually adapted EBCR program for patients with CHF in China or other similar settings where EBCR services are scarce.

Research questions:

1. What is the current evidence regarding TCEs for the rehabilitation of exercise capacity and QoL for CHF patients (**Paper I**)?

2. Is *Baduanjin* intense enough to produce physiologically oriented outcomes for CHF patients (**Paper II**)?

3. What is the feasibility of the BESMILE-HF program for CHF patients (**Paper III**)?

4. What are participants' experiences when using doing *Baduanjin* (**Paper IV**)?

4 METHODS

4.1 OVERVIEW

This project has been established under the framework of Medical Research Council guidelines for developing complex healthcare interventions [91]. Based on this framework, **Paper I** and **Paper II** belong to the development phase of the intervention; and **Paper III** and **Paper IV** belong to the pilot phase of the intervention.

Paper I was a systematic review and meta-analysis of 33 RCTs involving 2,465 patients with CHF. Both English and Chinese databases were searched from their inceptions to October 23, 2019. RCTs were included if they compared the addition of TCEs into routine managements to routine managements alone; or compared TCEs to general exercise, with routine managements as a consistent co-intervention in both groups. Data were screened and extracted independently using predesigned forms. RCT quality was assessed with the Cochrane tool. The primary outcomes were peak oxygen consumption (VO_{2peak}), 6MWD and MLHFQ.

Paper II was a descriptive study. Twenty patients with CHF with NYHA II~III volunteered for this study. Participants were examined during two separate sessions, with 1 to 2 weeks between sessions. During session one, a symptom-limited CPX was performed on a cycle ergometer for measurement of maximal exercise capacity. During session two, participants performed one 9-minute round of *Baduanjin* with continuous measurement of VO_2 and HR. Measurements obtained during the *Baduanjin* were compared to data obtained during cardiopulmonary exercise testing.

Paper III included a pilot RCT. Eighteen patients with CHF were recruited from the GPHCM: 8 in a BESMILE-HF group and 10 in a control group. Both received the usual medications, with the intervention group receiving additionally the BESMILE-HF program for 6 weeks. Feasibility was explored by participants' involvement in the intended intervention. Clinical outcome assessments were conducted at baseline and post-intervention, while adverse events were captured throughout the study period.

Paper IV was a qualitative study nested in the pilot RCT. After the pilot RCT ended, seven participants in the intervention groups were invited to take part in the interview. All interviews were conducted face-to-face using native language in the cardiac rehabilitation room at the hospital. A semi-structured interview guide developed based on a review of the relevant literature was used. All questions were open-ended, and follow-up questions were used to gain a deeper understanding of areas that appear essential for each individual. On average, the interviews lasted for around 40 minutes.

4.1.1 Setting: Guangzhou, Guangdong Province, China (Paper II~IV)

Research referred to **Paper II~IV** was conducted in Guangzhou, China. Guangzhou is the capital of Guangdong province and the 3rd largest Chinese city (**Figure 4**). It is located in Southeast China and has a permanent population of 13.5 million with more than 7 million permanent residents in its urban areas [92].

The cardiac rehabilitation remains insufficiently implemented in current clinical practice in Guangzhou city. Firstly, there is a low availability of cardiac rehabilitation services, especially in the outpatient clinics [5]. Secondly, the practice patterns of cardiac rehabilitation is poorly standardized [5]. In the vast majority of cases, cardiac rehabilitation is in the form of verbal information supplemented by leaflets and booklets emphasizing early mobilization and the identification and control of risk factors [50]. In addition, most programs that do exist are coordinated by a nurse, but relatively few used other healthcare professionals such as exercise physiologists, dieticians or physiotherapists which are recommended in the current guidelines [50]. Thirdly, there is no cardiac rehabilitation referral system after hospital discharge. Hence, there are still very few cardiologists who commonly add cardiac rehabilitation in their daily clinical practice for their patients [5].

The GPHCM is one of the oldest and largest hospital groups of Chinese medicine in China. It has four branch hospitals in different urban districts of Guangzhou, and a total of 3,150 beds. Over 100,000 patients are admitted to GPHCM each year. The sample were taken from cardiology outpatient clinics and cardiology inpatient departments at each of the four hospital branches (Figure 4).

Figure 4 Settinng for Paper II~IV

4.2 STUDY PROTOCOL

4.2.1 Study selection (Paper I)

One reviewer (XC) scanned all titles and abstracts to exclude irrelevant citations which were checked by a second reviewer (YC). Two reviewers (XC and YC) independently assessed the eligibility of the remaining citations after retrieving the full texts of potentially relevant articles. RCTs were included, and selection criteria conformed to the PICOS approach, as described below.

Population. Patients diagnosed with HF that were in a stable phase of the disease with no acute exacerbations. There were no restrictions regarding heart failure subtypes.

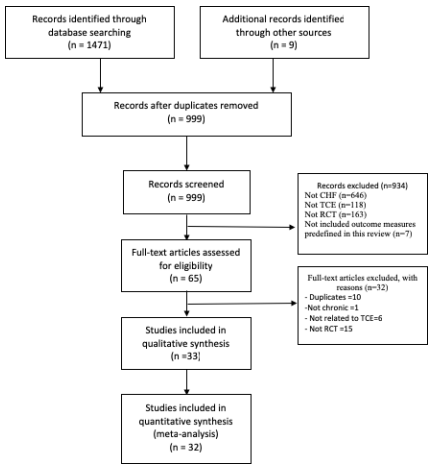
Intervention. RCTs that applied an intervention group receiving any form of TCEs (e.g., TaiChi, Liu-Zi-Jue, Ba-Duan-Jin, Wu-Qin-Xi, Yi-Jin-Jing) were included. However, studies were excluded if TCEs had been used in combination with other oral traditional interventions such as Chinese herbal decoctions.

Comparators. No exercise or general exercise which is planned, structured, and repetitive for the purpose of conditioning the body (such as walking, cycling, swimming, or running). Routine management were provided according to clinical guidelines and as a consistent co-intervention to both groups.

Outcomes. Primary outcomes included: (1) VO_{2peak}; (2) 6MWD; (3) QoL (MLHFQ). Secondary outcomes included: LVEF, B-type natriuretic peptide (BNP), and other clinically relevant outcomes; as well as adverse events and participant's adherence to TCEs.

In total, 1,480 records were retrieved from database searches. After excluding duplicates, 999 potentially relevant abstracts were screened, and 934 were excluded for failing to meet the inclusion criteria. The remaining 65 full texts were read, and 33 RCTs [80-82, 84, 85, 93-120] (24 in Chinese [80-82, 85, 95-98, 100-103, 107-117, 120] and 9 in English [84, 93, 94, 99, 104-106, 118, 119]) were deemed eligible for this systematic review. Quantitative synthesis was performed with 32 RCTs by pooling the results through a meta-analysis (**Figure 5**) [121].

Figure 5 A flowchart of the study selection process in systematic review (Paper I)



4.2.2 Participants (Paper II~IV)

Paper II~IV used the same inclusion and exclusion criteria to recruit participants [8]. The following four criteria had to be fulfilled for inclusion in the study: (i) aged 18 or above; diagnosed with CHF; (ii) clinically stable, defined as symptoms/signs that have remained generally unchanged for ≥1 month; and (iii) slight to moderate limitation of physical activity defined as NYHA classification of II or III (**Appendix 1**).

Exclusion criteria. (i) Patients who have contraindications to exercise testing or exercise training; (ii) patients who have serious acute or chronic disease affecting major organs or mental disorders; (iii) history of cardiac surgery, cardiac resynchronization therapy, intracardiac efibrillation, or implantation of combined device within the previous 3 months; (iv) history of cardiac arrest within 1 year; (v) history of peripartum cardiomyopathy, hyperthyroid heart disease, or primary pulmonary hypertension; (vi) inability to perform a bicycle stress test; (vii) severe cognitive dysfunction precluding understanding of exercise concepts; (viii) current participation in either Baduanjin or a conventional cardiac rehabilitation program; or (ix) participation in a concurrent trial.

For **Paper II**, twenty participants (age: 65±10 yrs., males: n=17) with NYHA II~III volunteered for this study. Participants had a clinical history of HF for 4±3.5 years and classified as either NYHA II (n=17) or NYHA III (n=3). The mean LVEF was 46.7± 12.1%, and they were either HFrEF (n=6), HFpEF (n=8), or (HFmrEF (n=6). In addition, 75% of participants (n=15) had been taking β-blockers (**Appendix 2**).

For **Paper III**, recruitment took place at GPHCM from August to November 2017. Potential participants were identified for eligibility assessment by 1) on-site screening at clinic visits; 2) regular screening of potential participants using electronic medical records; and 3) referrals from physicians. A total of 322 individuals were identified. Of these, 47 (14.6%) were approached and screened for eligibility, and 36 (77%) met pre-defined criteria. Finally, a total of 18 (50% of those eligible) patients agreed to participate and were then randomized **(Figure 6)**. The majority of the participants were male (94%) with a mean age of 68 (SD: 10). Clinically, half were NYHA Class II, and the other half were NYHA Class III; 9 (50%), 4 (22%), and 5 (28%) patients were HFrEF, HFmrEF, and HFpEF, respectively. Beta-blockers were used by 89% of the participants. The intervention and control groups were comparable on all demographic and clinical characteristics, expect for history of coronary heart disease (**Appendix 3**).

For **Paper IV**, after the pilot RCT ended, eight participants in the intervention groups were invited to partake in a semi-structured interview. Seven participants agreed to be interviewed within two weeks. The age of the seven interviewed participants ranged between 61 and 72 (mean age 67 years). All were male and married. In this sample, two participants had finished primary school, one had finished secondary school, and four had attained college or university degrees (**Table 2**).

Figure 6 Flowchart of the pilot study (Study 3, Paper III)

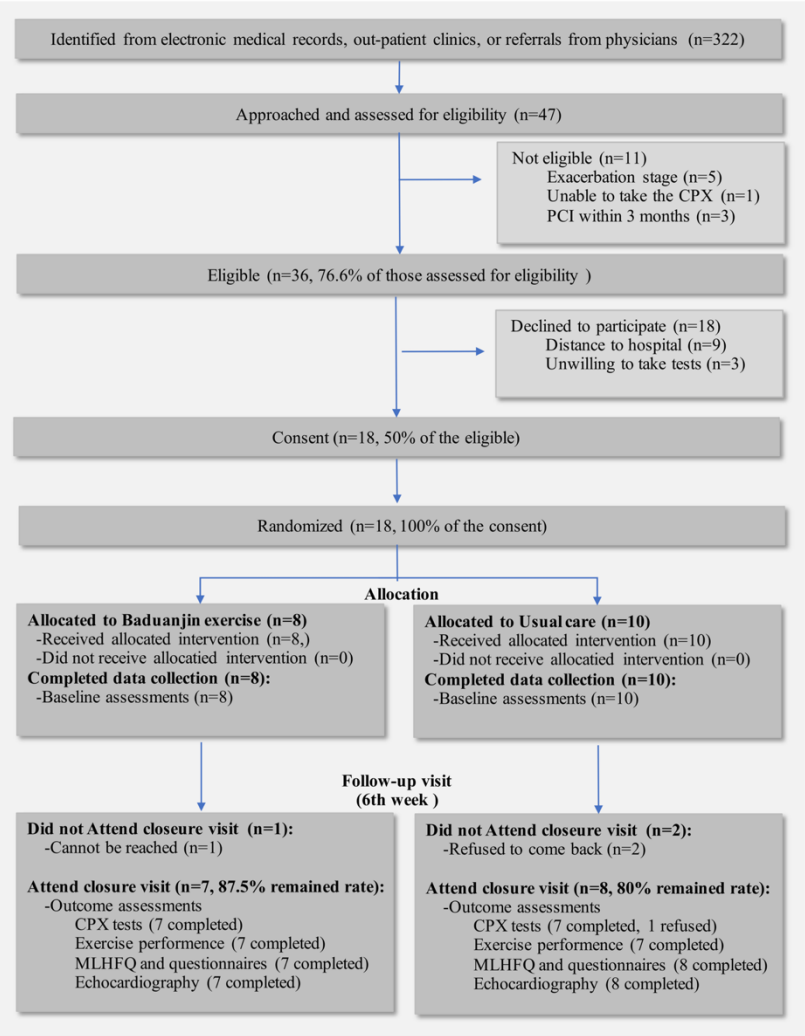
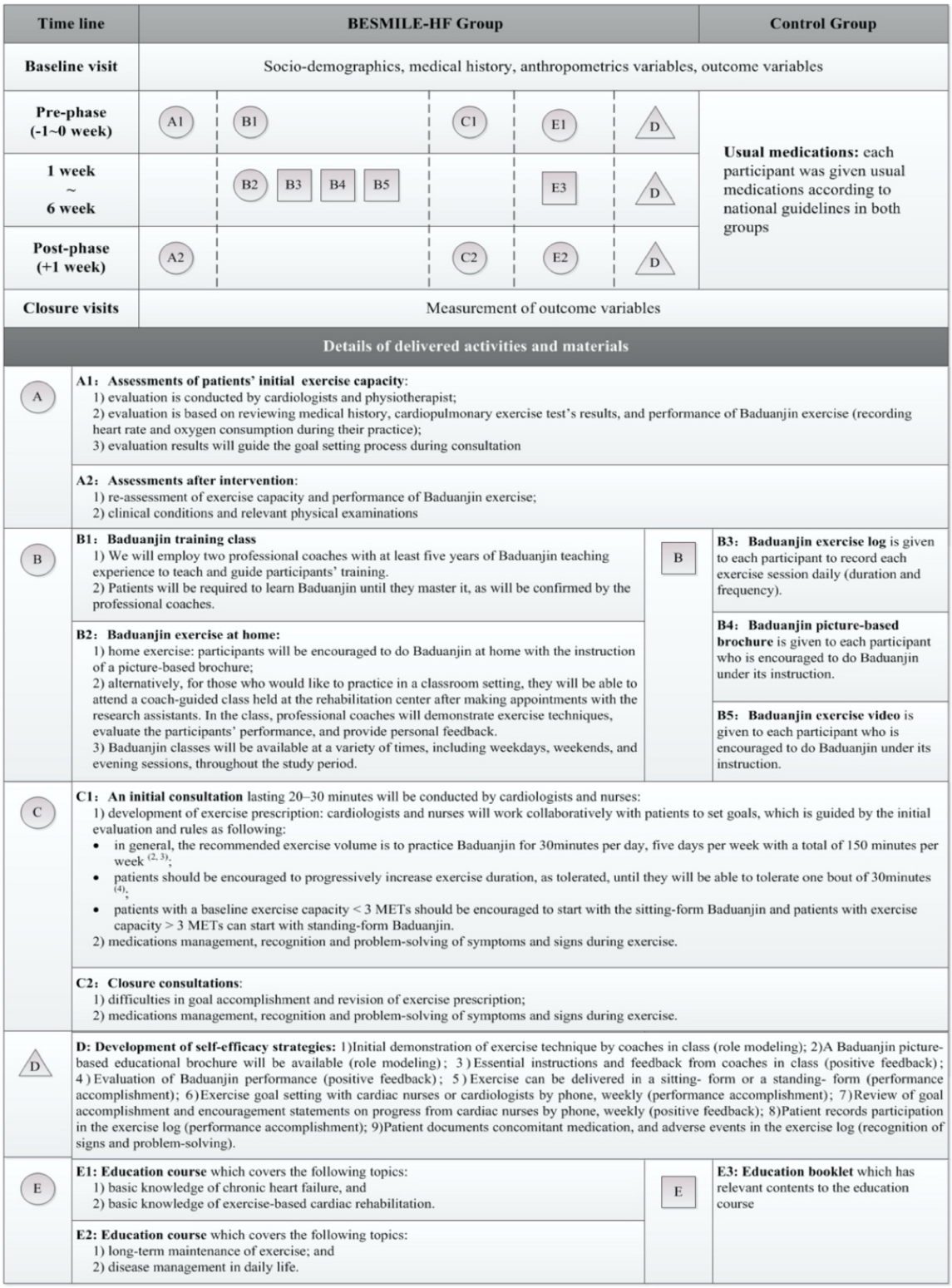


Table 2 Interviewed participants in Paper IV (n=7)

ID	Sex	Age	Education level	NYHA class	LVEF sub-type	Exercise time ≥ 30min/day?
	Male	67	College	II	HFrEF	Yes
6	Male	71	High school	III	HFpEF	Yes
8	Male	68	College	II	HFrEF	Yes
10	Male	62	Primary	III	HFpEF	Yes
14	Male	72	College	II	HFpEF	Yes
15	Male	71	College	II	HFrEF	No
20	Male	61	Primary	III	HFrEF	Yes

Figure 7 Graphical depiction of the BESMILE-HF program and the research schematic process for both groups, and data collection. (Activities are represented by circles o reflect their flexibility and materials by squares to reflect their fixed nature. Different components are labelled with different letters. Below the diagram, a legend gives a brief description of each component)



4.2.3 Procedures (Paper II)

Each participant visited the hospital on two separate sessions. During the first session, a maximal exercise test was conducted to determine individual maximal exercise capacity. On the same day, participants were required to learn how to practice *Baduanjin* until they had mastered it. The standing-form of *Baduanjin* from China's General Administration of Sport [61] was used in this study. One professional coach with over five years of teaching experience, taught and confirmed participants' technique. Patients were then required to practice on their own at home for 1-2 weeks following the instructions of a video with verbal hints. Therefore, a period of at least 7 days separated the two visits, and all experimental procedures were completed within 2 weeks. On the second visit, a *Baduanjin* intensity test evaluated the cardiopulmonary responses during *Baduanjin*.

4.2.4 Intervention and control (Paper III)

Both groups received the usual medications in accordance with national guidelines for 6 weeks[122]. Patients in the control group received only the usual medications according to national guidelines. This is because patients typically do not receive EBCR in this setting [5].

In the BESMILE-HF group, patients also received the pilot BESMILE-HF program. A graphical depiction of the intervention is shown in **Figure 7**. It included the core components of the full-scale 12-week BESMILE-HF program. Before the start of the 6-week home-exercise period, participants attended an exercise course to learn the eight postures at the hospital. A professional coach confirmed their performance. Following the exercise course, participants attended an educational course covering topics related to CHF, as well as exercise on the same day. Initial evaluation was conducted by the cardiologist by reviewing medical history, clinical examination results, and *Baduanjin* performance. Once the evaluation report was finalized, the initial consultation session was conducted by the cardiologist and the cardiology nurse. They would explain the exercise prescription and the results for the initial evaluation following pre-defined outlines. This was followed by 6-weeks of home exercise with guidance and instructions from a *Baduanjin* exercise demonstration video, a graphical exercise brochure, and weekly follow-up. Participants were generally required to do *Baduanjin* 30 minutes per day, five days per week, resulting in a total of 150 minutes per week. This was tailored according to individual evaluation results. Patients were asked to record their exercise performance in an exercise log (including duration in minutes and frequency) daily throughout the study period. After 6 weeks, participants were contacted to return to the hospital to attend the closure evaluation- and consultation-sessions.

4.2.5 Randomization, allocation concealment and blinding (Paper III)

Patients were informed and provided the possibility to ask questions before they signed a consent form. Eligible patients were randomized into either a BESMILE-HF group or a control group. A block randomization sequence was generated by SAS 9.2 (SAS Institute Inc., Cary, NC, USA) in a 1:1 ratio. In the pilot RCT, treatment allocation was conducted using sealed and numbered envelopes. We had made 20 numbered envelopes (a target sample size of 20

participants). As we were able to include 18 participants, hence only the first 18 envelopes were used. Given the nature of the intervention, it was not possible to blind the patients and personnel involved in conducting the programs. Outcome assessors, laboratory technicians, data managers, and statisticians were blinded to treatment allocations.

4.3 DATA COLLECTION

4.3.1 Data extraction of systematic review (Paper I)

One reviewer (XC) used a standardized form to extract data from the included articles. The following data were extracted: study characteristics (e.g., author, year, country), participant characteristics such as age, sex, sample size, NYHA functional class, LVEF sub type, interventions (e.g. types, frequency, durations, target intensity of TCEs) and controls, as well as outcomes measured. Attempts were made to contact the original investigators regarding any missing data. The extracted data was checked by a second reviewer. Any discrepancies were resolved by agreement after rechecking the source papers and further discussion with a third reviewer.

4.3.2 Maximal exercise test (Paper II ~ III)

The maximum exercise test was conducted according to the ATS/ACCP Statement on Cardiopulmonary Exercise Testing [123]. This was a symptom-limited exercise test using a bicycle ramp protocol: initial work rate of 0 watts with 10% predicted maximum work rate increments every minute. Participants were verbally encouraged to maintain the desired pedal rate of 60 rpms and to exercise until exhaustion or fatigue. However, the examiner would stop the test according to the established criteria [124]. Perceived exertion was measured using the 6-20 Borg Scale (every 2 to 3 min) throughout the test. The exercise test time ranged from 8-12 minutes. Heart rate (HR) and rhythm were continuously monitored by 12-lead electrocardiogram. Peripheral oxygen saturation was continuously monitored and blood pressure was measured at rest and every 3-minutes until test termination. HR (bpm) and oxygen consumption (VO_2, mL/kg/min) were collected automatically from the system for each participant (averaged over 10 seconds).

4.3.3 Baduanjin intensity test (Paper II)

Baduanjin intensity test was conducted on the second visit. Prior to the test, all subjects were instructed to lie down and rest in a supine position for 30 minutes. During the test, participants were required to practice one round of *Baduanjin* lasting 9 minutes under the instruction of a video with verbal hints on technique to ensure that the same posture, pace, and sequence were followed. The VO_2 were measured simultaneously while breathing room air through a face mask covering the nose and mouth. Inhaled and exhaled gases were analyzed in real time with a metabolic cart. In addition, HR were continuously monitored. Blood pressure was measured at rest and every 3-minutes until test termination.

4.3.4 Clinical outcome measurements (Paper III)

The following clinical outcomes were collected at baseline and follow-up at the 6th week during an assessment appointment at GPHCM's Heart Failure Center. Details of outcome measurements have been reported previously[8].

Cardiorespiratory fitness. We used a CPX to measure exercise capacity (4.3.2) [8].

Balance and mobility. The timed up-and-go test was performed [125] and patients were required to stand up from a 45-centimeter high chair, walk 3 meters at a comfortable pace, turn 180°, return to the starting point, and sit again. This test was timed with the use of a standard stopwatch by a research assistant blinded to the treatment arm.

Self-efficacy for exercise (SEE). The participants will be instructed to listen to nine different situations, and then to choose an option from 0 (not confident) to 10 (very confident) that represents their perception of confidence regarding engaging in regular exercise. A validated Chinese version of the SEE will be employed in this trial [126].

Disease-specific QoL. The disease-specific QoL was self-assessed by the MLHFQ. This validation instrument consists of 21 items rated on six-point Likert scales, representing different degrees of impact of CHF on QoL, from 0 (none) to 5 (very much). It provides a total score (range 0–105, with a lower number denoting better QoL). A validated Chinese version of the MLHFQ was employed in this trial [127].

Generic QoL. Generic QoL was self-assessed by the EQ-5D-5L questionnaire which has been used previously to measure health status in patients with HF [128, 129]. In this pilot study, we only used the visual analog scale of EQ-5D-5L, a graph representation similar to a thermometer that ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). A validated Chinese version of EQ-5D-5L was employed in this trial [130].

Anxiety and depressive status. The Hospital Anxiety and Depression Scale (HADS) was self-administered to measure the presence of depression and anxiety. Participants were instructed to choose one response from the given answers that best describe their current feelings. The HADS is a 14-item self-report screening scale originally developed to indicate the possible presence of anxiety and depressive states in the setting of a medical out-patient clinic.

Echocardiography. Echocardiography parameters of cardiac function was assessed by the resting three-dimensional multi-view echocardiogram before the exercise program was initiated and upon completion of the program. Functional parametes such as LVEF as well as structural parameters related to diastolic/systolic/valvular status were also be collected.

Laboratory tests. Blood samples was collected to measure the levels of prognostic biomarkers (NT-proBNP) and inflammatory mediators (hsCRP). NT-proBNP and hsCRP were analyzed by the GPHCM lab.

Clinical events, such as hospitalizations and major adverse cardiac events (MACEs) and safety outcomes (adverse events), were captured throughout the study period.

4.3.5 Semi-structure interview (Paper IV)

Seven semi-structured interviews were conducted with participants. A female research assistant who is an attending physician with a background in cardiology was trained to conduct the interviews. All interviews were conducted face-to-face using native language in the cardiac rehabilitation room at the hospital. The interview guide was developed based on a review of the relevant literature [131, 132]. It contained open-ended questions in order to gain a deeper understanding of the experience of *Baduanjin*. The guide was pilot tested for clarity, relevance, and pertinence to the aim of the study and thereafter finalized by the research team. For the complete interview guide, refer to **Box 1**. The interviews were recorded and transcribed verbatim by the person who had conducted the interview. On average, the interviews lasted for around 40 minutes.

Box 1. Interview guide

1. Tell me about your experiences practicing *Baduanjin*.
2. How did you experience the exercise learning course?
   -What did you think of the coach?
   -Did you master the *Baduanjin* exercise?
3. How did you practice *Baduanjin* at home?
   -What you think of each *Baduanjin* posture?
   -What motivated you to practice? Or not to practice?
   -Describe whether you have had any unpleasant experiences (like injuries or pain) or barriers when practicing *Baduanjin*.
4. What did you think of the effects on your daily life after practicing *Baduanjin*? Is it beneficial to you?
   -If so, what benefits did you get?
   -If not, what might be the reasons?
5. Do you have any suggestions regarding this exercise?

4.4 DATA ANALYSIS

4.4.1 Quality assessment and certainty of evidence (Paper I)

In accordance with recommendations in the Cochrane Handbook, the trials' methodological quality was independently evaluated by two reviewers using the Cochrane risk of bias assessment tool. Any discrepancies were resolved by agreement after rechecking the source papers and further discussion with a third reviewer. The following domains were considered: (1) random sequence generation; (2) allocation concealment; (3) blinding of patients and personnel; (4) blinding of outcome assessors for primary outcomes; (5) incomplete outcome data; (6) selective reporting. The overall evidence and certainty of evidence were evaluated with the Grading of Recommendations Assessment, Development and Evaluation approach.

4.4.2 Meta-analysis (Paper I)

Mean differences (MD) and 95% confidence intervals (CIs) were calculated, heterogeneity was assessed with an I^2 statistic. A sensitivity analysis was conducted by removing each study individually to estimate the results' consistency. Subgroup analyses were performed according to different types of TCEs and program duration. Additionally, a post hoc subgroup analysis was conducted to explore heterogeneity originating from heart failure subtype (HFrEF or HFpEF).

4.4.3 Statistical analysis (Paper II ~ III)

For Paper II, data from the maximal exercise test and the average cardiorespiratory parameters obtained during *Baduanjin* were summarized as mean and standard deviation (SD). The mean VO_2 and HR collected during *Baduanjin* were compared to individual maximum exercise capacity and reported as a percentage (expressed as $\%VO_{2max}$ and $\%HR_{max}$).

For Paper III, continuous data were summarized as mean and SD, or as median and interquartile range (IQR); categorical data were summarized as counts and percentages. For outcome variables, a Wilcoxon signed-rank tests was used to examine changes from baseline to the 6th week within the groups. In addition, the analysis of the baseline, the 6th week, and change from baseline to the 6th week in the intervention group versus control group was conducted using the Mann–Whitney *U* test. Moreover, Spearman correlation was used to explore the relationship between baseline self-efficacy and patients' total exercise time. The level of significance will be set at $p < 0.05$.

4.4.4 Qualitative content analysis (Paper IV)

Qualitative content analysis based on an inductive approach was performed using the structure described by Elo and Kyngas [133]. The analysis was mainly done by two researchers (XC and HZ). First, all transcribed words were read several times to obtain a sense of the entire meaning. Then, the participants' subjective experiences after the Baduanjin training were extracted and combined. Third, the text was condensed and divided into different meaning units. The meaning units were further condensed and labelled with codes. Next, the various codes with similar content were sorted into subcategories categories. Then, the subcategories were sorted and formulated as categories. Finally, the categories were abstracted into themes.

4.5 ETHICAL CONSIDERATIONS (PAPER II~IV)

The studies was conducted in accordance with the Declaration of Helsinki, and the BESMILE-HF study has been approved by the Ethics Committee at the Guangdong Provincial Hospital of Chinese Medicine (number: B2016–202-01) and registered (ClinicalTrials.gov: NCT03180320). All patients were informed about the study, were given the possibility to ask questions and provided consent before participating in the study. Participants were told they could withdraw at any time.

5 RESULTS

5.1 SUMMARY OF EVIDENCE ON TCES FOR CHF (PAPER I)

The included RCTs were published between 2004 and 2019 [121]. The included RCTs involved a total of 2,465 CHF patients (age ranging from 52 to 74 yrs) with NYHA functional class ranging from I to IV. Sample size per RCT ranged from 16 to 180, 84% of whom were Chinese. States or regions of publication were China (n=25), Taiwan (n=2), the United States (n=5), the United Kingdom (n=1), Italy (n=1), and Sweden (n=1). Details of included RCTs are listed in table 1 from Paper I.

For the TCEs, researchers used Tai Chi in 17 RCTs; Qigong in 14 RCTs; as well as Tai Chi plus Qigong in the remaining two RCTs. Qigong included *Baduanjin*, *Liuzijue*, *Baduanjin* plus *Liuziju*, and *Chan-Chuang*. TCEs training time lasted from 15 to 60 minutes per session; and its program duration varied between 4 weeks (n=2), 8 weeks (n=1), 12 weeks (n=17), 16 weeks (n=3), 24 weeks (n=5), and 52 weeks (n=5).

Of note, training characteristics of TCEs regarding training intensity are rarely described adequately enough to evaluate the dose-response effects, i.e., to render the studies replicable, or to interpret the findings' validity and translate the interventions into practice**.**

In terms of the comparison, 26 studies compared TCEs plus routine managements against routine managements alone. Five studies compared TCEs against general exercises. There were two 3-arm studies that included two control groups comparing TCEs vs. general exercises vs no exercise. Generally, routine managements included standard pharmacological treatments in all of the RCTs; in some of the RCTs, it also included education, dietary counseling, and/or general exercise advice.

Evidence from RCTs indicated (with a moderate level of certainty) that the addition of TCEs into routine managements was associated with better QoL (MLHFQ), improved exercise capacity (VO_{2pek}, 6MWD), increased LVEF, as well as reduced BNP level, as compared with the routine managements alone. Low evidence certainty showed that TCEs were associated with larger improvement in QoL (MLHFQ) and exercise capacity (VO_{2peak}, 6MWD) than general exercise (**Figure 8**) [121].

Evidence was also found that TCEs is safe. There was high adherence to TCEs programs. The retention rate in the TCE groups ranged from 67%~100%. The six studies that included TCEs training classes reported attendance between 75%-89%.

Figure 8 Summary of finding of the systematic review (Paper I)

Outcomes (measurements)	Source				Effect Size			Level of Certainty	Certainty Assessment				
	Countries (year range)	NYHA	LVEF range	No. of Patients (RCTs)	Mean difference (95%CI)	I^2	Referred Figure		Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias
A. 「Taichi-Qigong-Practice plus RM」 vs 「RM」													
- Qualigy of life (MLHFQ) FU: 4~52 wks	China/Taiwan/ US/UK (2004 ~ 2019)	I ~ IV	22~60% (n=687) ≤50% (n=115) unknown (n=198)	1000 (14)	**-8.63 scores** (-10.60 to -6.67)	94%	Fig 2A	Moderate	Not serious	Serious[c]	Not serious	Not serious	Not serious
- Exercise capacity (6MWD) FU: 4~52 wks	China/Taiwan/ US (2004~2019)	I ~ IV	22~52% (n=865) unknown (n=551)	1416 (17)	**59.63 meters** (43.35 to 75.90)	88%	Fig 3A	Moderate	Not serious	Serious[c]	Not serious	Not serious	Not serious
- Exercise function (Peak VO_2) FU: 4~24 wks	China/US (2004~2018)	I~IV	22~42% (n=190) ≤50% (n=55)	245 (4)	**1.24 mL/kg/min** (0.91 to 1.57)	0%	Fig 4A	Moderate	Not serious	Not serious	Not serious	Serious[d]	Undetected
- Echocardiography (LVEF) FU: 4~24 wks	China (2010~2019)	I~III	30~52% ≤ (n=747) 50% (n=55) unknown (n=66)	868 (11)	**3.97 %** (1.22 to 6.72)	96%	Fig 5A	Moderate	Not serious	Serious[c]	Not serious	Not serious	Not serious
- Laboratory test (BNP) FU: 4~52 wks	China/US (2004 ~ 2019)	I ~ IV	22~49% (n=279) ≥50% (n=100) unknown (n=312)	691 (8)	**-76.12 , pg/mL** (-134.61 to -17.62)	95%	Fig 6A	Moderate	Not serious	Serious[c]	Not serious	Not serious	Undetected
B. 「Taichi-Qigong-Practice plus RM」 vs 「General Exercises plus RM」													
- Qualigy of life (MLHFQ) FU: 8~12 wks	China/US (2013~2018)	I~III	52~65% (n=34) ≥40% (n=109) unknown (n=60)	203 (4)	**-9.18 scores** (-17.95 to -0.41)	86%	Fig 2B	Low	Serious[a]	Serious[c]	Not serious	Serious[d]	Undetected
- Exercise capacity (6MWD) FU: 12~24 wks	China/ Italy/US (2011~2019)	I~III	31~65% (n=260) ≥40% (n=108) unknown (n=60)	428 (7)	**46.66 meters** (-18.17 to 111.49)	97%	Fig 3B	Low	Serious[b]	Serious[c]	Not serious	Serious[d]	Undetected
- Exercise function (Peak VO_2) FU: 12 wks	China/US (2013~2018)	I~III	62~65% (n=16) ≥40% (n=109)	125 (2)	**0.14 mL/kg/min** (-0.43 to 0.70)	0%	Fig 4B	Moderate	Not serious	Not serious	Not serious	Serious[d]	Undetected
- Echocardiography (LVEF) FU: 12~24 wks	China/US (2013~2019)	I~III	31~65% (n=273) ≥40% (n=109)	382 (4)	**3.17 %** (-1.25 to 7.59)	0%	Fig 5B	Moderate	Not serious	Not serious	Not serious	Serious[d]	Undetected
- Laboratory test (BNP) FU: 12~24 wks	China/US (2013~2019)	I~III	31~65% (n=136)	136 (2)	**61.29 pg/mL** (-52.22 to 174.79)	77%	Fig 6B	Low	Not serious	Serious[c]	Not serious	Serious[d]	Undetected

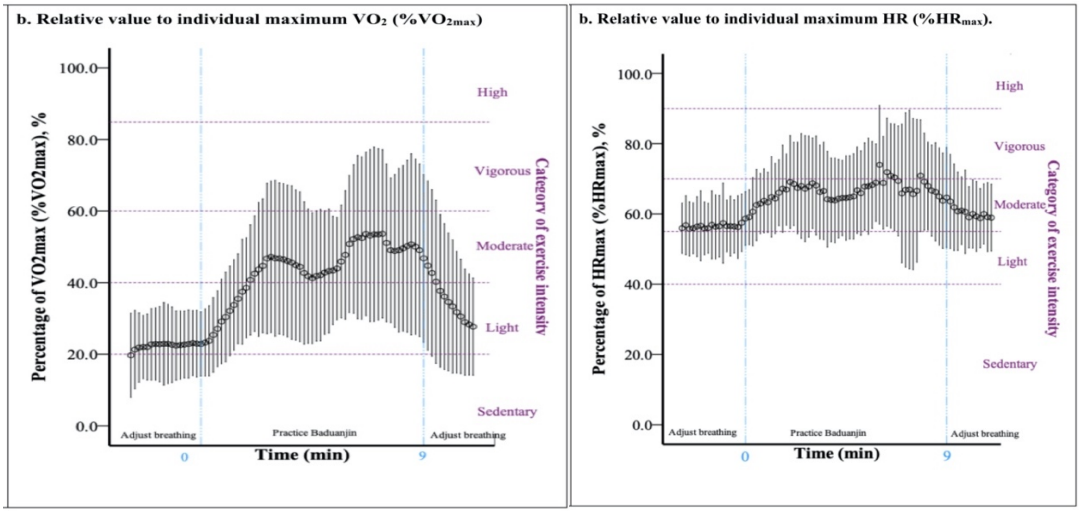
a. 30% of the information from 1 High risk RCT; removing this RCT significantly altered the effect estimates, 25% of the studies had high risk of randomization process. **b**. 20% of the information from 1 High risk RCT; removing this RCT moderately altered the size of effect estimates, 17% of the studies had high risk of randomization process. **c**. Considerable heterogeneity based on I^2. **d.** Imprecision, as OIS criteria was not met, primarily due to the small sample size (<400). **6MWD:** 6-minute walking distance, **BNP:** B-type Natriuretic Peptide, **CI:** confidence interval, **FU:** follow-up, **LVEF:** left ventricular ejection fraction, **MLHFQ:** Minnesota Living with Heart Failure Questionnaire, N**YHA:** New York Heart Association, **Peak VO2:** peak oxygen consumption, **RCT:** randomized controlled trial, **RM:** routine management (according to current guidelines).

5.2 BADUANJIN'S INTENSITY

In our study **(Paper II)**, the individual absolute intensity was 2.0±0.4 METs (ranging from 1-3 METs). This categorized *Baduanjin* exercise as a light-intensity activity (1.6-3 METs) if it is practiced by healthy individuals. However, both measures of relative intensity as measured in this study, $\%VO_{2max}$ and $\%HR_{max}$, categorize *Baduanjin* as a moderate-intensity exercise. In addition, a bimodal pattern response related to semi-squat postures was observed for VO_2 and HR. Moreover, the mean energy expenditure was 155.4±29.6 kcal/h. Therefore, average energy expenditure was estimated to be 23.3±4.4 kcal for one 9-minute Baduanjin session.

Baduanjin training intensity fulfilled ACSM's recommendations to stimulate the body, causing physiologically-oriented outcomes [134]. While performing *Baduanjin,* the mean VO_2 and HR were 7.1±1.2 mL/kg/min and 86.1±15.2 bpm, respectively. Compared to the cardiopulmonary exercise test, the VO_2 was 44% of their VO_{2max} and 67% of their HR_{max}, categorizing *Baduanjin* as a moderate-intensity exercise Moreover, both of the response lines were mostly located within the recommended moderate-intensity zones (**Figure 9**).

Figure 9. VO_2 and HR response [9].



In addition, most of the participants said that its gentle and slow movements provided a suitable intensity level for the elderly (**Paper IV**).

> *This exercise, to be honest, the amount of exercise is not too much. The elderly can still bear it; I am a bit tired and have a slight heating sensation, and it made me sweat. This feeling is similar to that when I swam before. But now I am unable to swim due to my medical condition. So, I think I can train my body with this exercise without being afraid of exercising too much.*

5.3 FEASIBILITY OF BESMILE-HF PROGRAM AND PARTICIPANT EXPERIENCES

5.3.1 High fidelity to intervention

Our results showed that the BESMILE-HF program was feasible with relatively high adherence and fidelity to protocol (P**aper III, Figure 10)**. All patients participated in the *Baduanjin* course which lasted for about 2 hours and their performances were confirmed by the professional coach, except for 2 patients who preferred to learn the exercise via the video (attendance rate: 75%). In terms of other part of the BESMILE-HF program, all patients took the education course at baseline and at 6th week except one patient (overall attendance rate: 87.5%). All patients underwent baseline assessment-session which included the collection of general assessments as well as individual cardiorespiratory data of *Baduanjin* exercise performance, except for 2 patients had only the general assessment data. All patients participated to the baseline consultation-session which mainly includes development of exercise prescription. For the closure assessment- and consultation- sessions, all patients participated except one who died within 6-week (attendance rate: 87.5% for both sessions).

The experience of learning *Baduanjin* was further explored by the qualitative study. Our participants said that, at the beginning of training, the *Baduanjin* exercises were easy to learn and did not required too much skill. They mentioned that *Baduanjin* consisted of only eight simple postures involving the whole body (**Paper IV**).

Nevertheless, they also though that mastering them (achieving a correct execution) took time and diligent practice (**Paper IV**). As they familiarized with the postures, they experienced the importance of reaching postural accuracy. They reported that the maximum training effects were difficult to achieve in cases where the exercises had been done incorrectly.

In addition to postural accuracy, the coordination of the mind, the movements, and breathing in *Baduanjin* can only be achieved over time through repeated practice. Participants said that it was essential to be aware of their bodies and how they felt during practice. (**Paper IV**).

Figure 10 Participants involvement in the BESMILE-HF program (n=8)

5.3.2 Good adherence

Baduanjin home-practice data was not available from two patients as one was lost to follow-up and the other did not return the exercise log. As a home-based EBCR program, the intervention group demonstrated exceptional compliance with the required exercises (**Paper III**). On average, participants exercised 27.5 (SD: 11.4) minutes/day and 5.6 (SD: 2.6) days/week for 6 weeks, reaching both the general required daily exercise time (30 minutes/day) and exercise frequency (5 days/week), respectively (**Figure 10)**. Moreover, the total home-practice times (mins) had a significant positive relationship with their baseline self-efficacy for exercise as measured by the SEE-C instrument ($r=0.831$, $p=0.006$).

The factors that facilitate exercise adherence were further explored in the qualitative study Participants said that, in the beginning, the reason they continued the exercises was the belief that *Baduanjin* can improve one's general health. With the progression of *Baduanjin* training, participants emphasized that its perceived training benefits were the predominant motivation for them to adhere to it. Furthermore, participants often referenced that "nobody can force me to exercise". Whether or not to exercise is one's own choice and this is determined primarily by the degree to which they care for their own bodies (**Paper IV**).

> *I benefit from Baduanjin otherwise I would not have participated for so long.*
>
> *Being able to walk without getting out of breath…motivated me more... "*

In addition to those intrinsic motivations, several external facilitators were also reported to have supported participants' sustained exercise (**Paper IV**). Our participants found that an exercise demonstration video was a necessary tool to guide participants' at-home exercise, especially at the outset when they were not so familiar with all eight postures. Participants reported that scheduling exercise or integrating it into their routine was useful for adherence. They also appreciated that the self-paced and equipment-free nature of the exercise allowed them to do it anytime and anywhere. A large training space or other auxiliary apparatuses were unnecessary. Some participants recommended *Baduanjin* to their friends and family members because they felt it was more enjoyable to practice together. Moreover, keeping exercise log was viewed as being helpful in keeping on track with their practice and reminding them to exercise daily.

> *It is convenient for me to practice Baduanjin. I even recommended it to my friends who also have heart disease. Sometimes I practice at the park with my friends and we all enjoy it. Since I retired, this has been a good opportunity to have something to do with them. This made me more willing to go and practice.*

5.4 CLINICAL OUTCOMES AND PERCEIVED BENEFITS

5.4.1 Exercise capacity

In the pilot study (**Paper III**), the control group demonstrated a significant decline in peak oxygen consumption (MD: -2.6, 95% CI -4.3 to -0.9) whereas, the BESMILE-HF group maintained their exercise capacity (MD: -1.2, 95% CI -1.2 to 0). Although the between-group difference was not statistically significance, there was a clear clinical improvement in the BESMILE-HF group (1.5 mL/kg/min, 95% CI: -0.3 to 3.2 versus minimal clinically important difference of 1 mL/kg/min).

More importantly, most of the participants stated that they had become more active in their daily life as they experienced less shortness of breath (**Paper IV**).

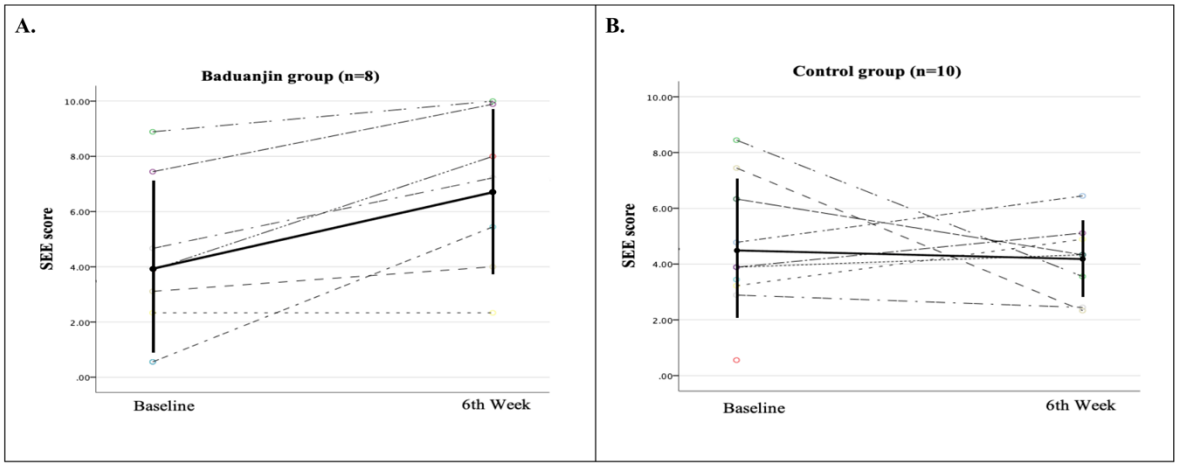
5.4.2 Self-efficacy for exercise

In the pilot study (**Paper III**), after 6 weeks, SEE scores improved significantly in the BESMILE-HF group (MD: 2.3, 95% CI 0.7 to 3.9, p=0.028, **Figure 11A**), but decreased slightly in the control group (MD: -0.9, 95% CI -3.2 to 1.4, p=0.377; **Figure 11B**). When comparing the score changes between the two groups, a significant difference was found for the SEE (MD: 3.2; 95% CI 0.6 to 5.9; p=0.04).

This finding was supported by the results of the interviews (**Paper IV**). Participants said that they gained confidence walking longer distances or at faster speeds, or even just had the confidence to get out of the house:

> *I used to keep crutches in my backpack, and I had to walk on crutches at all times. Now, I can walk without crutches. Sometimes I can walk more than 20,000 steps, and sometimes I will challenge myself to see how far I can go.*

Figure 11 Change in exercise SEE from baseline to 6 weeks in the A) intervention group (n=8) and B) control group (n=10)



5.4.3 QoL and other clinical outcomes

In the pilot study (**Paper III**), no significant differences between groups, for either post-intervention values or changes, were observed for: QoL; any echocardiography parameters except FS%; biomarkers such as NT-proBNP and hsCRP; balance/mobility as measured by Timed up-and-go test; or status of depression/anxiety (**Appendix 4**).

However, participants experienced improvements in their physiological and mental health (**Paper IV**). In terms of physical health, some participants mentioned that their digestion had gradually improved, and they had better appetites after participating. Some participants had suffered from intractable constipation for several years, but now have regular bowel movements without constipation. Participants noticed that their sleep had improved, their sleep time was extended, and they fell asleep quicker.

> *I think my digestive system has become stronger and now I have a better appetite. Recently, I have been eating more than I did in the past. Moreover, I was often constipated before, but now I no longer suffer from constipation…I used to be scared to sleep. After a few weeks of Baduanjin qigong training, I could fall asleep as soon as I lay down.*

Moreover, participants experienced better moods and had become hopeful about their lives. (**Paper IV**). All participants reported feeling comfortable every time they finished practicing Baduanjin. They also felt relaxed, as they said Baduanjin made them calm, pleasurable, and anxiety-free. Some participants also said that they had obtained positive energy and vigour from Baduanjin.

> *Every time after I practice Baduanjin, I feel relaxed. I haven't been so relaxed in a long time. To be honest, after getting this disease, I lost confidence in myself and there was no hope in life. But after a period of exercise, I felt that my mental state was much better and more energetic than before, and my thoughts were not so negative.*

5.5 SAFETY ISSUE OF BADUANJIN

In the systematic review, no adverse event related to TCEs was found in the included studies, and patient dropout in the exercise groups was low, with most withdrawals being due to hospitalization or CHF exacerbation **(Paper I**).

In terms of the cardiopulmonary response during practicing Baduanjin, both averaged and instant intensity levels are under or close to the ventialtory threshold which fulfill the requirement of current clinical practice guidelines **(Paper II)**.

Throughout the pilot RCT, no adverse events related to the intervention were captured (**Paper III**). However, one patient in the BESMILE-HF group died due to heart failure exacerbation, and two patients from the control group experienced acute heart failure exacerbation resulting in hospitalization (**Paper III**).

6 DISCUSSION

The overall aim of this project was to provide knowledge, experience, and evidence on how to deliver a contextually adapted EBCR program for CHF patients in China. This was addressed through a systematic review of current evidence, a descriptive study to confirm *Baduanjin* intensity, a pilot RCT to evaluate the feasibility of the BESMILE-HF program, and a qualitative study to explore participants' experience with *Baduanjin*. The main findings are:

1. Based on moderate-level evidence, adding TCEs into routine pharmacotherapies was associated with statistically significant improvements in exercise capacity and QoL. When compared to general exercise, we found superior improvements in the TCE group; they were significant for QoL, but not for exercise capacity (with a low level of certainty). We also found evidence that TCE is safe, and has high adherence.

2. Both measures of relative intensity, $\%VO_{2max}$ and $\%HR_{max}$, categorize *Baduanjin* as a moderate-intensity exercise. *Baduanjin*'s moderate intensity make it suitable for improving exercise capacity in CHF patients. In addition, the VO_2 and HR responses both exhibited a bimodal pattern during the exercise session. Further, the average energy expenditure was estimated as 23.3 kcal for a 9-minute *Baduanjin* session.

3. The BESMILE-HF program was well received by patients. As a home-based EBCR program, the intervention group demonstrated exceptional compliance with the required exercises. We also found that one's initial self-efficacy had a positive effect on the total exercise time. More importantly, intervention may improve participants' exercise self-efficacy and may improve exercise capacity.

4. Participants said that the *Baduanjin* postures were easy to learn, but that the coordination of the mind, the movements, and breathing in *Baduanjin* could only be achieved progressively through repeated practice. They also perceived that regular high-quality *Baduanjin* practice provides many benefits for both the mental and the physical health of CHF patients. Moreover, the perceived training benefits played a crucial role in adherence to home-based training.

6.1 INTERPRETATION OF FINDINGS

6.1.1 TCEs is a promising rehabilitation exercise for CHF

QoL and exercise capacity are two domains of interest in rehabilitation research[135]. The positive results for MLHFQ suggest that TCE can improve CHF patients' QoL. Moreover, the pooled effects are also clinically significant, with the effect estimate exceeding the minimal important clinical difference of 5 points. [136] Our findings show that TCE's benefits are superior to those of general exercise at improving QoL (MD: -9.18). This has not been reported in earlier studies. The effect size is similar to that reported in a Cochrane systematic review (Long *et al.* 2019) [26] in which the reviewers compared all exercise interventions with usual care (-7.11 points, 95% CI -10.49 to -3.73).

We found a moderate level of evidence that the addition of TCEs into current practice benefits CHF patients' exercise capacity. We found positive results for the 6MWD, both in the overall pooling of 17 studies (60 meters); as well as in each of the subgroups. Our results are consistent with a previous systematic review of Tai Chi which reported a similar improvement of 50 meters [137]. The pooled improvements were also clinically relevant because they exceeded the minimum clinically important difference (>30 meters) [138]. We also found positive results for the VO_{2peak} which is the gold standard for assessing exercise capacity [19]. This reinforces how practicing TCEs benefits CHF patients' exercise capacity. Unlike findings from previous reviews which have reported that Tai Chi does not change the VO_{2peak} [137, 139, 140], there was a positive result for VO_{2peak} in the Tai Chi subgroup in our study. Our meta-analysis involves two more recent RCTs [95, 110] which were not included in those previous meta-analyses. This results in a larger sample size. In addition, we have restricted our attention to those studies without exercise controls. Studies with exercise controls, similar to the active-control in the pharmacological trials, are expected to have negative results, and the effects' estimates are usually smaller than those of placebo-control trials, especially for open-label studies. In addition, the magnitude of the pooled improvements from the TCE in VO_{2peak} and 6MWD were similar to those of the pooled improvements from conventional exercise modalities in other systematic reviews [141, 142].

6.1.2 Baduanjin's moderate intensity make it suitable for CHF

Firstly, the *Baduanjin* training intensity fulfilled ACSM's recommendations to stimulate the body, causing physiologically-oriented outcomes [134]. It has been recommended that the exercise intensity be set at 40%-50% of VO_{2max} or 50-60% of HR_{max} at the starting point when initiating an exercise-based rehabilitation program for CHF patients [62, 143]. Moreover, *Baduanjin* intensity level is similar to that of general exercises that are used in rehabilitation programs for CHF. A recently published Cochrane Systematic Review of EBCR for heart failure shows that most EBCR programs use moderate intensity training at 40-80% of HR_{max} or 50-85% of VO_{2max} [26]. Therefore, the benefits of exercise capacity should be expected from continuous practice, and previous studies have reported that *Baduanjin* improves exercise capacity [80-85].

Exercise intensity can be expressed as either an absolute, for example, heart rate or metabolic equivalent (MET), or as a relative measure such as $\%VO_{2max}$ or %HRmax allowing for comparison to other forms of exercise. A challenge when categorizing exercise intensity using absolute measurements is inter-individual variability with regards to functional capacity. Hence, the intensity of one exercise may differ across the population and may exceed the capabilities of some individuals [144]. Therefore, we believe that continuous monitoring of $\%VO_{2max}$ and $\%HR_{max}$ responses is an appropriate way to provide a composite gauge of exercise intensity, with priority given to $\%VO_{2max}$ due to the HR modulating effect of pharmacotherapies often prescribed for CHF patients (e.g.β-blockers).

Secondly, *Baduanjin* is a safe exercise for CHF patients which can be practiced in a home-based setting. Both *Baduanjin's* averaged and instant intensity levels are under or close to the

ventilatory threshold which fulfills the requirements of current clinical practice guidelines. The key element of *Baduanjin*, mindful breathing, emphasizes the coordination of breathing and physical movements, relaxation, focused self-awareness, and imagery. This decreases cardiac sympathovagal tone and ventricular workload [72], decreasing the training burden on patients. Therefore, the likelihood of significant adverse arrhythmia, ischemia, and/or other adverse cardiovascular events is proportionally reduced.

Thirdly, *Baduanjin* can facilitate initiation of exercise, long-term exercise adoption and maintenance. Our results show that the average VO_2 during *Baduanjin* was 44% of participants' VO_{2max} and the average HR was 67% of subjects' HR_{max}. Moreover, we observed a bimodal pattern response related to semi-squat postures for VO_2 and HR. These findings indicate that patients can achieve a suitable level of intensity during training by adjusting their postures, such as modifying the height of the semi-squat posture. Prior studies have shown that exercise efficacy is more likely with a regimen that can provide effective low-intensity options, particularly as exercise is initiated, but that can also intensify as tolerated, or facilitate intermittent intervals of higher intensity [145-147]. In this respect, *Baduanjin*, which is inherently less strenuous, but easily modified to tailor intensity, may address tolerability and accessibility.

6.1.3 The BESMILE-HF program and Baduanjin is feasible for CHF

The BESMILE-HF program's feasibility is primarily attributed to its in-home nature and the use of traditional *Baduanjin* exercise. Compared to other low-cost outdoor activities such as walking, biking, running, and swimming, a home-based modality might be a more attractive and sensible option for optimal EBCR flexibility, given that one-third of Chinese HF patients have difficulty or are unable to leave their homes due to their symptoms [43]. In addition, *Baduanjin* is an adaptable form of exercise that can be practiced in any place, and at any time. It also requires no special equipment and is not time-consuming. Hence, it is easy to incorporate into daily routines.

Adherence to exercise programs is generally low among CHF patients, which may limit their effect on clinical outcomes [148]. In practice, self-efficacy is crucial to adherence [87]. In this thesis we found a statistically significant positive relationship between baseline self-efficacy scores and individual exercise time. This result is supported by emerging literature in which self-efficacy is reported as the dominant factor in exercise uptake and maintenance among the CHF population [149]. Therefore, it is reasonable to assume that the BESMILE-HF program would increase participants' adherence and maintenance of exercise compliance over time.

It is important to highlight that there was a significant improvement in self-efficacy score in the intervention group, but not in the control group. The between-group difference was found to be statistically significant, even within the context of this pilot study. However, the lack of periodic contact with doctors or nurses in the control group could have resulted in bias since the frequent contact with rehabilitation staff may explain some of the improvement in the intervention group. Nevertheless, a recent RCT reported that 16-week *Baduanjin* training can

improve self-efficacy for managing chronic disease in community-living adults, such as increasing confidence to mitigate fatigue, physical discomfort/pain, and emotional distress, and enabling the completion of various tasks and activities [145]. Our results also dovetail with previous evidence which shows that Tai Chi, a similar style of exercise, can improve CHF patients' self-efficacy [105].

6.1.4 Positive experience of using Baduanjin

Baduanjin is an aerobic exercise with simple, slow and relaxing movements. With different skill levels, people may perform the same style of *Baduanjin* in different ways, which may in turn lead to variegated physiological responses. A previous study has shown that skill level may have a considerable effect on metabolic and cardiorespiratory responses to Tai Chi practice (a traditional exercise similar to *Baduanjin*) [150]. The authors find a higher mean heart rate and deeper breathing among the high-level practitioners. In our study, many participants experienced difficulty achieving maximum training effects if *Baduanjin* was practiced incorrectly. A high-level practitioner can perform *Baduanjin* with high quality, especially for the handful of movements which are particularly difficult. For example, high-level *Baduanjin* practitioners tend to perform those movements requiring participants to squat with lower positioned technique better than low-level practitioners, thus requiring increased muscle contraction from the lower extremities. Therefore, the improvements in their exercise capacity are expected to be more apparent. As most of the participants in this study were new to *Baduanji*n, we identified several challenges to reaching postural accuracy. These suggested that additional instructions should be added to the teaching course or demonstration videos in clinical practice.

The coordination of the mind, the movements and breathing in *Baduanjin* can only be achieved progressively through repeated practice. Unlike other forms of exercise, *Baduanjin* involves both 'internal' and 'external' effort, so as to train both the body and the mind. While practicing *Baduanjin*, the practitioner not only has to move his or her body, but circulate *qi* (vital energy) inside the body via breathing. While practicing *Baduanjin*, a high-level practitioner should breathe in harmony with the movements, so as to circulate *qi* around the body. An ordinary-level practitioner, on the other hand, would not do it in this way, because he or she would only have to concentrate on his or her movement, and keep his or her breath natural. Moreover, with practice, a beginner will gradually be able to concentrate his or her mind on each movement he or she performs; however, only by attaining a certain level can he or she coordinate breathing and movements with the guidance of conscious mental effort [6]. Hence, this implies the need for more guidance and explanation on the connection between mind, body, and breathing for *Baduanjin* practitioners in future studies.

In terms of mental health, *Baduanjin* can relax, calm, and please practitioners' minds, and therefore improve psychological and mental health. From the perspective of Chinese medicine, the circulation of *qi* is intertwined with psychological and mental health. Negative psychological states such as anger, depression, irritability, and restless mood may cause *qi* stagnation. An underlying philosophy of the practice is that *Baduanjin* cultivates the balance

and harmony of *qi* to maintain a healthy body [59]. *Baduanjin* focuses on mobilizing functional potentialities, regularizing the breathing process, and unifying the mind and body by regulating breathing, thereby promoting the normal circulation of *qi* [151]. The normal circulation of *qi* can also regulate passive emotions. In terms of biological mechanisms, it has been reported that the activity and connectivity of key brain regions related to depression, the autonomic nervous system, and neuro-inflammatory sensitization can be modulated by mind-body exercise [152, 153]. Similarly, an interview study of 20 informants who practiced *Baduanjin* 40 minutes daily for 12 weeks reiterated that they felt relaxed psychologically, due to self-tranquility, pleasure, and relief from emotional symptoms [154].

Our qualitative findings regarding intrinsic motivation to do *Baduanjin* provide insight into the good adherence found in this sample. 'Intrinsic motivation' refers to the inherent satisfaction individuals derive from physical activity, including feelings of enjoyment and accomplishment [155]. Intrinsic motivation has been defined as the inherent satisfaction that drives one to undertake a particular activity [155]. Motivation is a critical factor in supporting sustained exercise, which in turn is associated with important health outcomes. In the interview, adherent participants often referenced their improvements in terms of walking further and improved mood by participating in *Baduanjin* training. It appears that actual and perceived improvements in health may be key mechanisms behind long-term exercise adherence. This echoes the findings of a qualitative study regarding exercise adherence in patients with CHF [156]. The author found that patients with CHF tended to be motivated by improved health and performance in daily activities [156]. Thus, when working with patients with CHF that are starting an exercise program, highlighting improvements can support long-term exercise adherence. Our findings also demonstrate the importance of autonomous regulation in fostering physical activity. Adherent participants mentioned that whether to exercise was one's own choice, and that this was primarily decided by the degree to which they cared for their own bodies. This highlights the need to examine the goals and self-regulatory features associated with regular participation in exercise and physical activity.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Strengths

Each study has its strengths. For **Paper I**, the systematic review was supported by a team that included an experienced reviewer, a subject specialist, and an information scientist with advanced knowledge of bibliographic search strategies. To avoid bias in the conducting and reporting of systematic reviews, the research question and inclusion criteria were established before conducting the review, and the study protocol has been published in PROSPERO (CRD42018081982). A systematic search strategy, before commencing the literature search, is fundamental to appropriate and successful information retrieval. Keywords and/or MESH terms were developed carefully and by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. We performed a comprehensive literature search. Multiple databases (PubMed, Cochrane library, EMBASE, CINAHL, and the Chinese database CNKI) were searched, including both the English and the Chinese literatures. There were two independent data extractors, and a consensus procedure for disagreements was in place. We assessed quality with the Cochrane risk of bias tool, and the evidence was graded with GRADE. We expected that studies with exercise controls, similar to the active-control in the pharmacological trials, would have negative results, and that the effects' estimates would tend to be smaller than those of placebo-control trials, especially for the open-label studies. When we conducted the meta-analysis, we pooled the studies separately according to comparators: (A) TCE plus routine management vs. routine management: to evaluate TCE's add-on effects; and (B) TCE plus routine management vs. general exercises plus routine management: to contrast TCE and general exercise. In addition, we conducted sensitivity analysis by removing each study one-by-one; the results maintained their consistency.

For **Paper II**, this is the first study to investigate *Baduanjin* intensity based on VO_2 and HR, as well as cardiopulmonary responses during *Baduanjin* among CHF patients. The findings on *Baduanjin* intensity are strengthened by comparison to maximal cardiopulmonary exercise testing (%VO2max and %HRmax response). In addition, for each participant, we conducted a maximal exercise test and a *Baduanjin* test at the same time of day. All tests were conducted by the same examiner to avoid inter-examiner variability. The examiner was both trained in, and experienced with, the tools.

For **Paper III**, the main strength is the use of RCT-design. The trial was also registered at ClinicalTrials.gov: NCT03180320) and the study protocol was published and followed [8]. The BESMILE-HF program is a complex intervention with several interacting components. This means that there will be a certain number of behaviors required by those delivering or receiving the intervention, as well as difficulties. Evaluations of clinical outcomes are often undermined by problems such as intervention delivery, recruitment and retention, and smaller-than-expected effect sizes [91]. Therefore, a pilot RCT was a suitable research method for evaluating the feasibility of the BESMILE-HF program.

Moreover, we also collected data regarding additional exercises that participants do beyond the *Baduanjin* in two ways: (1) step counts, and (2) self-reported questionnaires. The step count was measured using an accelerometer (Garmin Vivofit) that we provided to each participant, both in the intervention and the control groups. Participants were required to wear the step count all day throughout the study period. Patients returned the step counts, and the ensuing data was downloaded by the research assistant. In addition, physical activity was self-reported using the validated Chinese version of the International Physical Activity Questionnaire short-form [157] at the baseline and at the 6th week. We found that both self-reported vigorous and self-reported sedentary activities were comparable between groups at baseline, as well as at the 6th week. Moreover, there was no significant between-group difference in objectively measured walking steps throughout 6 weeks or in self-reported time spent walking (51.4±14.6 vs. 57.5±31.8 mins per day) throughout the 6-week period. Walking has been reported to be the dominant exercise among CHF patients, and is the most likely factor influencing outcome variables. In this respect, the influence from additional exercise is balanced between both groups.

The pilot RCT only considered the variation between *Baduanjin* and clinical outcomes via quantitative measurement. It is important to obtain a more in-depth description of the *Baduanjin* experience. Hence, the use of qualitative research methods is another strength for this thesis (**Paper IV)**. Firstly, information regarding the relationship between *Baduanjin* and the practitioner's subjective experience might present new outcomes. For example, although the *Baduanjin* is deem to be learner-friendly, challenges reaching postural accuracy for postures requiring participants to squat, bend their waist, or turn their head were reported. Moreover, participants also though that mastering the postures (achieving a correct execution) and coordinate the mind, movements and breathing took time and diligent practice. Secondly, With a growing appreciation for patient-centered outcomes, it has been recognized that patient experience is just as important as physiological tests and measurements. For example, although we did not significant results on most of the quantitative clinincal outcomes, participants perceived improvement in their physical and mental health after 6 weeks. Lastly, qualitative research, which collects data on participants' lived experiences, is the ideal tool for detail experiences that are difficult to capture through quantitative research, and expand our scientific knowledge beyond what can be learned quantitatively [158]. For example, participants reporting perceived training benefits played a crucial role in adherence to their home-based training. This qualitative finding might explain the good adherence found in the pilot RCT.

In addition, we took several steps to enhance the findings' credibility (**Paper IV)**. To achieve dependability, we read the interviews several times to get an overall understanding, and there was also constant comparison between the parts of the analysis and the complete interview texts. All interviews were conducted by one researcher (HZ), which also added to the results' dependability and reduced the risk for a biased interview procedure. To achieve confirmability, several researchers with different backgrounds were involved in the analysis process and discussed the findings. This minimized the risk of inventing data or biased interpretation.

6.2.2 Limitations

6.2.2.1 Heterogeneity (systematic review)

In the systematic review (**Paper I**), the interpretation of the results may be challenged by the heterogeneity observed. Sensitivity analyses by TCEs styles or durations revealed some sources of heterogeneity, but were unable to account for all of the variation. For example, practitioner expertise, heart failure etiopathogenesis, NYHA classification, and patients with different cultural backgrounds were each revealed to be potential sources of heterogeneity. As many individual or combined factors may have influenced heterogeneity, this study did not succeed in identifying the reasons for this. Secondly, the descriptions of the 33 RCTs regarding the randomization method, allocation concealment, and blinding evaluation were neither detailed nor comprehensive. Therefore, certainty of evidence was downgrade due to the above-mentioned limitation.

6.2.2.2 Participant characteristics

Most of the study population was male. Sex has been shown to be an influencing factor in the change in exercise capacity and time spent on exercise [148, 159] (**Papers II** and **III**). Although all participants were encouraged to elaborate upon their perspectives on the research topic, it is possible that female or elderly patients with HF could have different perceptions on *Baduanjin* (**Paper IV**). Secondly, all participants in **Paper II** were new to *Baduanjin,* enabling a similar skill level among participants. However, whether intensity and cardiopulmonary responses vary among those who are more skillful remains unknown.

6.2.2.3 Blinding of the intervention

Although we blinded outcome assessors, blinding of patients was impossible. participants could identify their allocated group. Trials with inadequate blinding are likely to exaggerate treatment effects, especially with regard to subjective results (such as SEE and QoL) and with participants with knowledge of traditional Chinese culture.

6.2.2.4 Self-report home-practice

Although the intervention group completed the required home exercises as reported through exercise logs, it should be noted that self-reported practice exercise tends to be overestimated. [149] Assessing and ensuring adequate levels of intervention adherence is a challenge in most self-directed home-based interventions. However, self-reported exercise records, because of their ease of use, remain one of the most common tools for recording exercise data. [149] Future, full-scale clinical trials should consider use of objective data collection methods to validate self-reported exercise data.

6.2.2.5 Small sample size

Given the scope of the pilot study and limited resources, the sample size was small. Therefore, the pilot RCT was not powered to test efficacy. However, the primary aim of the pilot study in **Paper III** is to explore intervention feasibility, such as the recruitment rate, data collection

process, and retention rate. Moreover, there is no data available regarding the BESMILE-HF program, this small size study can still provide us some information regarding the preliminary efficacy of this intervention.

6.2.3 Generalizability/Transferability

Even considering the limitations mentioned above, we still believe that our main findings described above are mostly transferrable to other parts of China. Firstly, the demographic and clinical characteristics of the study participants are similar to the those CHF patients undergoing a cross-sectional survey in Guangzhou [160] and in China as a whole [43].

Secondly, although we only recruited CHF patients with NYHA classification of II or III, the findings on *Baduanjin* intensity also apply to CHF patients in general. This is because patients with NYHA classification of II or III account for 83% of the HF patients in the stable stage in this setting (see Section 2.3.2) [43]. In addition, in terms of intensity of *Baduannjin*, a bimodal pattern in the intensity related to semi-squat postures for VO_2 and HR. Hence, patients with NYHA I or NYHA IV can also achieve a moderate training intensity by adjusting their postures, such as modifying the height of the semi-squat posture.

Thirdly, *Baduanjin* is commonly accepted as being beneficial to one's health and relatively easy to learn in a short time in the Chinese, it has been a community exercise throughout different regions of mainland China [161], Taiwan, Macau, and Hong Kong [162, 163]. Hence, feasibility and positive experience of practicing *Baduanjin* are expected to be found.

While this thesis leads to conclusions specific to mainland China, the findings may be relevant for countries with similar lifestyles and demographic profiles, especially those with limited medical resources. High-income countries and LMICs share similar barriers to EBCR which have been described at three inter-related levels: provider, patient and system [47, 48]. The most commonly reported barrier to EBCR is the lack of physician referral to EBCR. Patient-related factors cited were affordability, particularly due to insufficient insurance coverage; transportation difficulties, primarily driven by long distances to EBCR centers; unwillingness to attend EBCR; and priorities competing for patients' time. The most frequently reported system factor was insufficient personnel and resources. Therefore, a low-cost and home-based exercise modality such as *Baduanjin* could disseminate EBCR in LMICs and also increase the options for EBCR programs in high-income countries.

Given the in-home nature of the BESMILE-HF program, it should also be feasible to apply it in other parts of the world. One-third of Chinese CHF patients reported rarely leaving their homes due to their disease (see Section 2.3.2) [43]. This suggests that home-based exercise might be a more attractive and sensible option than outdoor activities for optimizing EBCR affordability and flexibility. Home-based exercise empowers patients to take responsibility and accountability for their own disease management [164]. Most importantly, it increases patients' access to EBCR by confronting the challenge of limited healthcare resources. This includes the paucity of rehabilitation facilities, the lack of medical reimbursement, and the poor access to hospital services in many rural areas[165].

It is difficult to render the studies replicable because *Baduanjin* coaches are not available in all parts of the world. However, with the proliferation of social media, tutorial videos produced by our research team are easy to find online [166, 167], and the certified version from China's General Administration of Sport is also available in English [168].

7 CONCLUSIONS

The main conclusions to be drawn from the work in this thesis are:

- TCEs may represent a promising rehabilitation therapy as an adjunctive to routine pharmacotherapies, or as alternative to conventional exercises for paitents with CHF.
- *Baduanjin*'s eight simple postures are not only accessible and learner-friendly, but also suitable for CHF as it is a moderate-intensity aerobic exercise without excessive cardiopulmonary burden.
- During practing *Baduanjin*, it is essencial for the practioner to coordinate the mind, movements and breathing in *Baduanjin* exercise, alongside ongoing correct execution.
- *Baduanjin* potentially promotes the overall physical and psychological health of CHF patients. However, a larger sample size and a longer follow-up period is needed to comfirm its benefit on clinincal outcomes.
- The integration of *Baduanjin* into a cardiac rehabilitation program may increase patients' long-term adherence to exercise by improving exercise self-efficacy.
- The integration of traditional *Baduanjin* in modern rehabilitation mightprovide CHF patients with a simple, inexpensive, and widely practicable EBCR delivery model which has the potential to be scaled up throughout China.

8 RECOMMENDATIONS

8.1 IMPLICATIONS FOR CLINICAL PRACTICE

- *Baduanjin* may represent a promising rehabilitation therapy as an adjunctive to routine pharmacotherapies, or as an alternative to conventional exercises for paitents with CHF.
- *Baduanjin* may have value in improving CHF patients' prognosis. In addition, *Baduanjin* can facilitate exercise initiation, long-term exercise adoption and maintenance.
- Compared with conventional aerobic exercise, *Baduanjin* consists of easier to learn movements with lower physical demands. They are also easier to perform at home without any assistive equipment and can improve CHF patients' cardiovascular circulation function. Thus, clinicians can instruct patients to exercise at home after discharge.
- Instructions of the details of each posture should be added to the teaching course in clinical practice. In addition, the guidance and explanation on the connection between mind, body, and breathing for *Baduanjin* practitioners is needed. An online system can be developed to guide patients in learning and practicing *Baduanjin* at home.
- Our findings regarding the energy expenditure have implications for the personalization and standardization of using *Baduanjin* for CHF patients. Two sessions of *Baduanjin* daily over 12 weeks might work better in improving peak VO_2 for CHF patients.

8.2 RECOMMENDATIONS FOR FUTURE RESEARCH

Our findings suggest several research gaps that future research could address:

- The majority of TCE trials have been conducted among the Chinese population. This raises the question of whether there might be varied cultural attitudes and acceptance of this kind of exercise in other countries. In addition, future studies should include participants with high symptom burdens or advanced HF.
- Future research is needed, with greater skill level heterogeneity to investigate the cardiopulmonary responses of *Baduanjin* in CHF patients, and to explore how *Baduanjin* characteristics, such as the postures, practice sessions, or practice skills influence intensity and cardiopulmumonary response.
- It is hard to discern the "true" effects of *Baduanjin* on clinical outcomes in our thesis. The reported improvements might come from BESMILE-HF, which would include other interactions between clinicians and participants. To see if the exercise itself improves the lives of heart failure patients, the control group should also receive similar interaction with optimizing medical therapy to answer this question.
- As the connection between the mind and body is a complex phenomenon, the role of *Baduanjin* and other forms of TCE in the heart failure population is still in need of elucidation.
- Multicenter RCTs with large sample sizes are needed to assess the effects of TCEs among CHF patients. The long-term effectiveness of TCEs for patients with CHF should also be evaluated. Theories about how TCE could treat patients with CHF and prevent such diseases should be the subject of additional future research.

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11 APPENDIX

Appendix 1 New York Heart Association (NYHA) Functional Classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix 2 Participants' characteristics in Paper II (n=20)

Characteristic	Mean±SD or Number (%)
Demographic and anthropometrical characteristics	
Male	17 (85)
Age, years	64.6 ± 9.9
BMI	24.5 ± 3.6
Weight, kg	67.5 ± 11.5
Smokers	12 (60)
Heart failure characteristics	
Heart failure history, years	3.8 ± 3.5
NYHA classification	
- NYHA II	17 (85)
- NYHA III	3 (15)
LVEF classification	
-HFrEF	6 (30)
-HFmrEF	6 (30)
-HFpEF	8 (40)
NT-proBNP, pg/mL	1116.2 ± 2335.8
LVEF(Simpson), %	46.7 ± 12.1
PASP, mmHg	27.1 ± 7.0
β-blocker users	15 (75)
Comorbidities	
Coronary heart disease	15 (75)
Previous Myocardial infarction	7 (35)
Atrial fibrillation	4 (20)
Hypertension	10 (50)
Type2-Diabetes	6 (30)
Hyperlipoidemia	8 (40)
Chronic kidney disease	2 (10)
Stroke	3 (15)
Peripheral vascular disease	12 (60)

Characteristic	Mean±SD or Number (%)
Cardiorespiratory parameters (VT/Max)	
RER	1.3±1.8 / 1.2±0.1
WR (watt)	54.9±22.5 / 93.1±33.3
VO_2/kg (mL/kg/min)	11.9 (2.7) / 17.6±4.9
HR (bpm)	101.6±17.0 / 131.6±18.0
METs	3.4±0.8 / 5.0 ±1.4
SBP (mmHg)	151.3±25.6 / 176.2±31.4
DBP (mmHg)	85.7±13.4) / 109.9±69.6
O_2 pulse (mL/beat)	8.1±2.5 / 9.2±3.2
RR (1/min)	25.0±5.0 / 33.5±4.9
V_E (L/min)	26.5±4.6 / 50.1±12.3
$P_{ET}CO_2$ (mmHg)	34.9±5.4 / 32.6±7.4

SD: standard deviation, BMI: Body Mass Index, NYHA: New York Heart Association, LVEF: left ventricular ejection fraction, HFrEF: heart failure with reduced ejection fraction, HFmrEF: heart failure with middle ranged ejection fraction, HFpEF: heart failure with perceived ejection fraction, HR: heart rate, bpm: beats per minute, SBP: systolic blood pressure, DBP: diastolic blood pressure, NT-proBNP: N-terminal B-type natriuretic peptide, PASP: Pulmonary artery systolic pressure. RER: respiratory exchange ratio, WR: work rate, VO_2: oxygen consumption, , HR: heart rate, bpm: beats per minute, O_2 pulse: oxygen pulse (the ratio of oxygen consumption to heart rate), METs: metabolic equivalents, SBP: systolic blood pressure, DBP: diastolic blood pressure, RR: respiratory rate, V_E: minute ventilation, $P_{ET}CO_2$: end-tidal carbon dioxide partial pressure.

Appendix 3 Participants' characteristics in Paper III (n=18)

	All n=18	Intervention n=8	Control n=10
Demographics			
Age, years	68±10	67±5	70±13
Male, n	17 (94)	8 (100)	9 (90)
BMI, kg/m^2	23±3	23±3	24±3
Smoking			
Never smoke, n	9 (50)	5 (63)	4 (40)
Previous smoker, n	7 (39)	2 (25)	5 (50)
Current smoker, n	2 (11)	1 (13)	1 (10)
Marital status			
Married, n	17 (94)	8 (100)	9 (90)
Widowed, n	1 (6)	0 (0)	1 (10)
Education			
Primary or less, n	6 (33)	3 (38)	3 (30)
High school or above, n	12 (67)	5 (62)	7 (70)
NYHA class			
NYHAII, n	9 (50)	5 (63)	4 (40)
NYHAIII, n	9 (50)	3 (38)	6 (60)
LVEF class			
HFrEF (EF<40%), n	9 (50)	5 (63)	4 (40)
HFmrEF (EF 40-49%), n	4 (22)	0 (0)	4 (40)
HFpEF (EF ≥50), n	5 (28)	3 (38)	2 (20)
Cardiac interventional procedure/surgical treatment			
PCI, n	11 (61)	6 (75)	5 (50)
Pacemaker, n	4 (22)	1 (13)	3 (30)
ICD, n	1 (6)	0 (0)	1 (10)
CRT/CRT-D, n	1 (6)	0 (0)	1 (10)
Valvular surgery, n	1 (6)	1 (13)	0 (0)
Repairment of V-/A-septal defect, n	1 (6)	1 (13)	0 (0)
Comorbidity			
Average comorbidities per patient, mean	4±2	5±2	3±1
Coronary heart diseases, n	13 (72)	8 (100)	5 (50)

	All n=18	Intervention n=8	Control n=10
Hypertension, n	11 (61)	6 (75)	5 (50)
Atrial fibrillation/flutter, n	6 (33)	3 (38)	3 (30)
Myocardial infarction, n	3 (17)	2 (25)	1 (10)
Stroke (Ischemic) , n	2 (11)	2 (25)	0 (0)
Hyperlipoidemia, n	5 (28)	3 (38)	2 (20)
Type2-Diabetes, n	11 (61)	5 (63)	6 (60)
Hyperuricemia, n	11 (61)	5 (63)	6 (60)
COPD/Asthma, n	1 (6)	1 (13)	0 (0)
Current cardiac relevant medications			
ACEI/ARB, n	17 (94)	7 (88)	10 (100)
Beta-blockers, n	16 (89)	8 (100)	8 (80)
Aldosterone blockades, n	16 (89)	7 (88)	9 (90)
Statins, n	16 (89)	8 (100)	8 (80)
Platelet anti-aggregants, n	14 (78)	8 (100)	6 (60)
Diuretics, n	10 (56)	3 (38)	7 (70)
Digoxin, n	5 (28)	3 (38)	2 (20)
Calcium antagonists, n	4 (22)	1 (13)	3 (30)
Anticoagulant, n	3 (17)	0 (0)	3 (30)

Results are presented as mean ± SD or n (%). BMI: Body Mass Index, NYHA: New York Heart Association, EF: ejection fraction, HFrEF: heart failure with reduced ejection fraction, HFmrEF: heart failure with mid-range of ejection fraction, HFpEF: heart failure with preserved ejection fraction, PCI: percutaneous coronary intervention, ICD: implantable cardioverter defibrillators, CRT/CRT-D: cardiac resynchronization therapy/with defibrillator, V-/A-: ventricular-or atrial-, COPD: chronic obstructive pulmonary disease, ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blocker.

Appendix 4 Results of clinical outcomes in Paper III

Outcomes	Control		Intervention		*P* value [E]
	Baseline	6th week[C,]	Baseline	6th week[C, D]	
1. CPX parameters					
Exercise test time, seconds	399 (309.8, 408.3)	329 (253, 419)	501 (400.8, 538.5)	404 (387, 488)	0.902
Wordload, watt	66 (53.3, 77.8)	70 (53, 85)	82.5 (65.8, 89.3)	82 (80, 85)	1
RER	55.5 (43.7, 59.5)	52.2 (40.3, 67.1)	60 (53.5, 68)	62.6 (62, 65.4)	1
VO_{2at}, mL/kg/min [a]	1 (1, 1.1)	1.1 (1, 1.3)	1.1 (1, 1.2)	1.1 (1, 1.2)	0.165
VO_{2peak}, mL/kg/min [a]	10.9 (8.9, 14.1)	9.7 (6.1, 11.6) C	12.9 (11, 13.6)	11 (10.3, 12.1)	0.128
VO_{2peak} %pred, % [a]	14.3 (10.2, 17.4)	13.6 (8.6, 15.2) C	15.9 (15.1, 16.8)	14.3 (13.6, 16.4)	0.295
HRR, bpm [a]	54.4 (49.4, 62.2)	47.6 (30.7, 51.7) C	59.2 (56, 62.6)	59.2 (50.6, 61.1)	0.128
Peak O_2 pulse, mL/beat [a]	29.5 (14.5, 42.5)	25 (11, 34)	35 (25.3, 47)	26 (16, 40)	0.097
V_E/VCO_2, slope [b]	8.1 (7, 10)	7 (6.4, 9) C	8.9 (7.6, 10.7)	10 (7.7, 11.1)	0.805
dVO_2/dWR, mL/min/W [a]	32.7 (29.1, 41.2)	36.7 (33.3, 42.9) C	32.9 (24.3, 35.9)	33.6 (28.2, 35.4)	0.073
FEV1 %pred, % [a]	7.4 (6.3, 8)	8.3 (4, 8.8)	7 (5.5, 8.7)	10.3 (9.4, 11.4) D	0.165
MVV %pred, % [a]	71 (60.8, 83.3)	68 (56, 87)	74 (54.5, 85)	78 (63, 82)	0.053
2. Self-efficacy for exercise					
SEE [a]	3.9 (3.1, 6.6)	4.3 (2.7, 5.1)	3.5 (1, 6.8)	7.2 (4, 9.9) [C, D]	0.04
3. Echocardiography					
LVEF, % [a]	41 (35, 47.8)	36.5 (34, 39.5)	34.5 (30.5, 50)	45 (36, 53)	0.281
FS, % [a]	24 (19.5, 30)	19 (17, 22.5)	21 (17.3, 28.8)	27 (18, 29) [D]	0.04
SV, mL/bit [a]	80 (64, 83.5)	82.5 (63.8, 92.8)	66 (57.8, 86.8)	83 (70, 97)	0.165
LVEDD, mm [a]	60 (51.8, 63.5)	64 (59, 67.5)	60 (49.5, 70)	59 (51, 67)	0.281

PASP, mmHg [b]	31 (19, 45)	26 (20.3, 36.5)	31 (25.8, 43.8)	27 (25, 32)	0.536
4. Biomarkers					
NT-proBNP, pg/L [b]	1177 (717.8, 2351)	872.9 (489.7, 4191.5)	1346 (268.5, 2686.3)	703 (289, 1062)	0.397
hsCRP, mg/L [b]	5.4 (1.1, 10.8)	6.2 (1.8, 15.9)	2.4 (0.5, 5.7)	1.6 (1, 4.4)	0.694
Total cholesterol, mmol/L [b]	4.3 (3, 4.6)	3.7 (3.3, 4.2)	4.2 (3.5, 4.4)	4.1 (3.6, 4.7)	0.072
LDL-C, mmol/L [b]	2.4 (1.7, 3)	2.2 (1.7, 2.7)	2.4 (2.2, 2.9)	2.7 (1.9, 3)	0.336
HDL-C, mmol/L [a]	1.2 (0.8, 1.6)	1.1 (0.8, 1.6)	1 (1, 1.2)	1 (0.9, 1.3)	0.152
Triglycerides, mmol/L [b]	1.3 (0.6, 1.8)	1.1 (0.7, 1.5)	1.5 (1.1, 2.2)	1.2 (1, 1.7)	0.536
Hemoglobin, g/L [a]	130.5 (124.3, 141.8)	137 (127, 147) C	134 (125.5, 142)	135 (131, 142)	0.731
5. Exercise performance					
Timed-Up and Go, seconds [b]	8.1 (6.5, 10.8)	8.6 (7.8, 10.7) C	7.1 (6.6, 9.8)	7.7 (6.9, 8.7)	0.094
Left-hand grip strength, kg [a]	28.6 (20.8, 35.5)	28.7 (22, 37.3)	29.7 (23.5, 32.2)	31.2 (26.1, 33.1)	0.536
Right-hand grip strength, kg [a]	31.8 (22.9, 37.6)	27.6 (23.9, 35.3)	29.9 (26.4, 33.1)	27.4 (23.6, 27.5) C	0.397
6. Quality of life					
MLHFQ total score [b]	20.5 (13.8, 65.5)	16.5 (3.3, 23.5)	12.5 (5.5, 31.8)	12 (1, 26)	0.779
EQ-5D-VAS score [a]	80 (73.8, 90)	86.5 (80, 98.8)	85 (64.8, 93.8)	75 (70, 100)	0.232
7. Depression & anxiety status					
HADS-anxiety score [b]	1.5 (1, 7)	1 (1, 3)	0.5 (0, 3)	1 (0, 6)	0.867
HADS-depression score [b]	1 (1, 3)	2.5 (1, 5.5)	1 (0, 6)	0 (0, 1)	0.072

Continuous data will be summarized as median and IQR. **a.** Higher value more favorable; **b.** Lower value more favorable; C. $p<0.05$, refers to the comparison with baseline using Wilcoxon signed-rank tests. **D.** $p<0.05$, refers to the comparison with the control group using Mann–Whitney *U* test at the 6th week. **E.** Between-group comparison of the changed scores using Mann–Whitney *U* test. CI: confidence interval, CPX: cardiopulmonary exercise test, RER: respiratory exchange ratio, METs: metabolic equivalents, VO_{2at}: oxygen uptake at AT, VO_{2peak}: peak oxygen uptake, HRR: heart rate reserve 1min post exercise, V_E/VCO_2: minute ventilation-carbon dioxide production, FEV1 %pred: percentage of predicted value of forced expiratory volume in 1 minute, MVV %pred: percentage of predicted value of maximum voluntary ventilation, LVEF: Left ventricular ejection fraction, FS: fractional shortening, SV: stroke volume, LVEDD: left ventricular end-diastolic diameter, PASP: pulmonary artery systolic pressure, NT-proBNP: N-terminal B-type natriuretic peptide, hsCRP: high-sensitivity C-reactive protein, LDL-C: low density lipoprotein-cholesterol, HDL-C: high density lipoprotein-cholesterol, MLHFQ: Minnesota Living with Heart Failure Questionnaire, EQ-5D-VAS: EQ-5D-visual analog scale, HADS: Hospital Anxiety and Depression Scale, SEE: Self-efficacy for exercise questionnaire.