Study Title: A strength-building lifestyle-integrated intervention for tackling double burden of sarcopenic patients with coronary artery disease: A pilot randomized controlled trial

Background

The world's older population continues to grow rapidly. More people survive into later life and living with multiple chronic diseases, including cardiovascular disease. Cardiovascular disease is highly prevalent among the older population, as more than 70% of the patients who develop cardiovascular disease by 70 years of age.[1] In particular the coronary artery disease (CAD), as a function of normal physiological age-related degeneration in the coronary arteries. CAD is characterized by atherosclerotic plaque accumulation in the coronary arteries, causing insufficient myocardial perfusion. CAD is a major burden of non-communicable disease that has reached an unequivocal pandemic status globally and regionally.[2] It is common for this vulnerable cohort to have multi-morbidity,[1] particularly those age-related conditions, such as sarcopenia.

Sarcopenia, a progressive and generalized skeletal muscle disorder characterized by accelerated loss of muscle mass and function, which is related to functional and physiological impairments.[3] It has emerged as a public health priority which affects 10% of the general older population.[4] Individuals with sarcopenia are associated with profound adverse health outcomes, including increased incidents of falls and fractures, functional decline and increased all-cause mortality.[5] The prevalence of sarcopenia increases to 31.4% among the individuals with cardiovascular disease, such prevalence rate is the highest when compared to people suffering from other comorbidities, including dementia, diabetes and respiratory disease.[6] Accumulating empirical evidence exists to indicate sarcopenia as an important prognostic factor in patients with CAD. A recent meta-analysis (N = 10) found that CAD patients with sarcopenia had more than a double of higher rate of major adverse cardiovascular outcomes (hazard ratio = 2.27, 95% confidence interval: 1.58 – 3.27) than the non-sarcopenic counterpart.[7] The biological mechanisms underpinning sarcopenia and atherosclerosis are yet to be fully elucidated, several shared pathophysiological and behavioral pathways appear to underlie the progression of both conditions, including endothelial dysfunction, arterial stiffness, inflammation and physical inactivity.[8] In particular, empirical studies reported more consistent association of lower limb muscle function with atherosclerosis in CAD patients, rather than the muscle function of upper limb.[9] The potential explanation may be related to the decline in lower limb muscle function results in reduced physical activity, which then lead to progression of both sarcopenia and atherosclerosis in patients with CAD. Furthermore, skeletal muscle acts as an endocrine organ which secretes myokines during muscle contractions. This bioactive substance protects coronary arteries against progression of atherosclerosis and stabilization of atherosclerotic plaques through anti-inflammatory effects.[10] Reduced myokines level jeopardizes such cardio-protective effects in sarcopenic CAD patients. Altogether, the vicious cycle between reduced muscle mass/strength and atherosclerosis underscores the urgency of managing sarcopenia in the population with CAD.

Currently, no drugs have proved to be effective and safe for treating sarcopenia.[3] Instead, clinical practice guidelines recommend exercise as the primary treatment for sarcopenia.[11,12] The evidence of resistance exercise in improving skeletal muscle mass and

strength in older adults with sarcopenia is especially compelling.[13] Nutritional support in terms of essential amino acids and high-protein supplements have also been used to manage sarcopenia in older adults. However, the clinical benefits of nutritional interventions without exercise are less clear. A recent network meta-analysis (N = 26)[14] examined the comparative effects of exercise, nutrition and combined exercise and nutrition interventions on health outcomes in older adults with sarcopenia. The findings indicated that both exercise alone and the combination of exercise and nutrition have beneficial effects on muscle strength and physical performance, but not nutritional interventions alone.[14] Physical inactivity is not only a major contributor to sarcopenia and negative health outcomes in older adults,[15] but also a significant predictor for the development and progression of CAD.[16] Aerobic exercise has been the focus for primary and secondary prevention for CAD. Indeed, resistance exercise, particularly low-to-moderate intensity [30-69% of 1-Repetition Maximum (1 R-M)], demonstrates similar or even greater beneficial effects on blood pressure and lipid profiles as compared to aerobic and high-intensity resistance training.[17]

Despite these encouraging findings on the beneficial effects of resistance-based exercise on sarcopenia and CAD separately, no study has been done to examine its effects on patients having the co-existence of sarcopenia and CAD, leaving a significant gap in the literature. Indeed, enabling this vulnerable cohort to adopt and maintain regular resistance exercise remains a great challenge. Older adults have reported perceived difficulty, time constraints and boredom as obstacles to resistance exercise.[18] An effective yet sustainable intervention needs to address these challenges/obstacles. Previous studies have highlighted the importance of enhancing older people's self-efficacy in performing exercise in order to improve exercise adoption and adherence.[19,20] Moreover, opportunities to resistance training, indeed, emerge around the clock in the routine of an individual. Assisting older adults to integrate exercise into daily activities can maximize the training benefits and overcome barriers to exercise, and thus improve exercise adoption and adherence.[21] Therefore, this study aims to develop a strength-building lifestyle-integrated intervention for sarcopenic CAD patients and to examine the feasibility and preliminary effects of this intervention on skeletal muscle mass, muscle strength, physical performance, cardiac-related functional status and health-related quality of life (HRQoL), psychological distress, major adverse cardiovascular and cerebral events (MACCE) and hospital readmission rates. Physical performance will be the primary outcome, while the remaining will be the secondary outcomes.

Research plan and methodology

Study design

This study will include an assessor-blinded two-arm prospective pilot randomized controlled trial (RCT) and a qualitative study to determine the feasibility, acceptance and engagement experience of the participants in the strength-building lifestyle-integrated intervention with assessments measured at baseline, 3 months and 6 months after randomization.

Study setting and participants

This study will recruit subjects in Care for Your Heart, a cardiac patient mutual support organization. Patients fulfilling the following eligibility criteria will be invited to join the study: 1) Chinese adults with a confirmed diagnosis of CAD; 2) age ≥60 years or older; 3) presence of sarcopenia according to the diagnostic criteria defined by the Asian Working Group for Sarcopenia[22]: low skeletal muscle mass (measuring the appendicular skeletal muscle mass with bioelectrical impedance analysis: <7.0 kg/m^2 for men and <5.7 kg/m^2 for women), accompanied by low muscle strength (handgrip strength <28 kg for men and <18 kg for women); 4) free from ischemic symptoms when performing activities of daily living; 5) living in the community. Patients who cannot read Chinese or with impaired cognition (Abbreviated Mental Test score ≤6) or communication, a pacemaker or implantable cardioverter defibrillator precluding the use of bioelectrical impedance analysis for body composition assessment, physical limitations precluding exercise training, with any contraindication for exercise, any terminal or unstable conditions (e.g., malignant arrhythmia, severe aortic stenosis, cancer), admitted or recently completed a structured cardiac rehabilitation program within the past 6 months will be excluded.

The sample size for this pilot study was estimated based on the primary outcome (i.e., functional capacity) to be measured by the Short Physical Performance Battery (SPPB). The literature indicated the minimal clinically importance difference is >1 point of SPPB[23] and the SD estimate is 4.2 in the population with cardiovascular disease, giving rise to the standardized effect size as 0.28. According to the method proposed by Whitehead et al.,[24] a sample size of 20 per study arm for the pilot study would give the future main trial 80% power at 5% level of significance to detect the between-group changes in the primary outcome at post-intervention time points. The total sample size is therefore 40. They will be randomly allocated in a 1:1 ratio, to receive the strength-building intervention or usual care. All participants in the intervention group will be invited to take part in a face-to-face qualitative interview to explore the feasibility and acceptability of the intervention. The interviews will be conducted individually in the center of the Care For Your Heart. Each interview will be audio-recorded and will last for approximately 60 minutes.

Control group: Usual care

The control group will receive routine care that they currently receiving provided by their primary healthcare providers, which include unstructured patient education on lifestyle modification. The usual care does not include structured exercise training.

Intervention group: A strength-building lifestyle-integrated intervention

Additional to the usual care provided by the primary healthcare providers, the intervention group will participate in a 12-week strength-building intervention to be delivered by an exercise specialist, who is required to have a Bachelor's degree in physical education, sports science, physiotherapy or equivalent, and at least 2 years of post-graduate experience. He/she will receive two weeks of training on sarcopenia and CAD, risk assessment and the exercise protocol. A blended mode of supervised and unsupervised community-based and online sessions, and telephone support will be used to optimize the training effects (Table 1). The training platform will be gradually shifted from in-person to online coaching, and then unsupervised self-practice with telephone support. The training schedule for

supervised sessions will last for 60 minutes per session, two sessions per week. Featuring with a lifestyle-integrated component of the intervention, the participants will be encouraged to self-practice the taught exercise skills on a daily basis by integrating into their daily routine.

The implementation is guided by an individualized, progressive, low-to-moderate intensity resistance-based exercise protocol, which has been designed according to the guidelines published by the American College of Sports Medicine,[25] guidelines for exercise prescription to reverse frailty[26,27] and the European College of Cardiology guidelines on exercise for patients with cardiovascular diseases.[28] Prior to the exercise training, the 10-Repetition Maximum (10-RM) test will be performed for estimating the 1-Repetition Maximum will be performed to guide the exercise prescription. A 3-phase approach, starting from familiarization, consolidation to habituation, will be adopted to enable participants to gradually incorporate resistance exercise into their day-to-day habit.

In the first two weeks of the familiarization phase, a community-based training will be adopted to let participants be familiar with the exercise protocol and to master the skills of the different types of resistance movements that can be done in everyday activities. The training schedule is 2 sessions per week and will take place in the community centers close to the participants' residential area in a small group format (4 participants/group). This training component will start with warm-up, followed by core exercise training, and cool-down exercise. A series of flexibility training and stretching will be performed during the warm-up and cool-down phases (15 minutes in total). The core exercise session will comprise balance and resistance (40 minutes) training, with 5 minutes break in between. The exercise protocol will include strength-building training with simple elastic equipment, such as elastic bands, cuff weights, and Gymstick™. Gymstick™ consists of a lightweight shaft and elastic tubing with foot straps connected to each end of the shaft. It is inexpensive, safe and can provide resistance training to all major muscle groups. Different resistance levels are available and the load on each Gymstick™ can be titrated by rolling the bar to shorten the elastic tubing. The resistance load will be individualized according to the periodically estimated 1-RM on a two-weekly interval. The resistance training will focus on large muscle groups over different body parts and will start with higher repetitions (e.g., 15 repetitions) at a lower intensity (30% of 1-RM) to build muscle endurance, confidence, and for mastering appropriate movement skills. This will progress to fewer repetitions (e.g., 7 – 8 repetitions) at greater intensity (i.e., 60 – 69% of 1-RM) to build muscle power. The progression will base on the OMNI scale, a validated 11-point perceived exertion scale for assessing the perceptions of exertion when performing resistance exercise.[30] The numbers on the scale represent a range of exertion levels from 0 (extremely easy) to 10 (extremely difficult). Patients' symptom status will also be monitored and the exercise intensity will be titrated to ensure patients are free from ischemic symptoms. Other exercise that can be integrated into everyday activities without special exercise equipment will also be included: single limb stance with and without arm, walking heel to toe, rock the boat, back leg raises, side leg raises, balancing wand, wall pushups, marching in place, toe lifts and calf stretches. Other than prescribing the number of repetitions and sets for these different forms of exercise, the participants will be equipped with the knowledge and skills about the strategies/principles to improve balance and strength in everyday activities. For instance, they are suggested to perform a tandem stance while watching television, and then upgraded to standing on one leg.

From Week 3 and 4, the exercise specialist will deliver supervised home-based training, with one in-person session via home visits and one session to be delivered remotely via an online platform (Zoom). Apart from ensuring the same training principles for the intensity as those in the community-based group training sessions, the exercise specialist will observe the home environment, explore the daily routine of patients and provide individualized advice on the integration of the exercise tasks into their daily activities. Then the supervision will gradually tail off from Week 5 and onwards, from online supervised sessions, to unsupervised self-practice sessions. To ensure proper progression of the training intensity, an in-person supervised home visit as a booster session will be given at Week 9, the beginning of the habituation phase. The remaining sessions in this phase will all be unsupervised self-practice sessions. Telephone follow-ups will be arranged at Week 10 – 12 by the exercise specialist, to offer continuous support and guidance to the participants. He/she will help participants to resolve any difficulties and barriers that they may encountered when integrating the exercise into their daily life. An exercise logbook will be used to document the exercise pattern of each participant.

Table 1. Schedule of the strength-building lifestyle-integrated intervention.

Phase	Week	Session 1	Session 2
Familiarization phase	1	In-person community-based exercise	In-person community-based exercise
	2	In-person community-based exercise	In-person community-based exercise
	3	In-person supervised home-based exercise	Remote supervised home-based exercise
	4	In-person supervised home-based exercise	Remote supervised home-based exercise
Consolidation phase	5	Remote supervised home-based exercise	Unsupervised home-based self-practice
	6	Remote supervised home-based exercise	Unsupervised home-based self-practice
	7	Unsupervised home-based self-practice	
	8	Unsupervised home-based self-practice	
Habituation phase	9	In-person supervised home-based exercise	Unsupervised home-based self-practice
	10	Unsupervised home-based self-practice + Tel support	
	11	Unsupervised home-based self-practice + Tel support	
	12	Unsupervised home-based self-practice + Tel support	

Fidelity monitoring and optimization

Various methods will be used to monitor and optimize the fidelity of the study intervention. Assessments and record forms will be use to document the exercise prescription and progression. Participants' attendance, exercise dose, performance and training response will be documented. A standardized manual will be developed to guide the delivery of each education session. The manual will also delineate the principles of exercise prescription and progression. Moreover, the 30% of the intervention sessions will be randomly selected

for fidelity monitoring by the principal investigator. Face-to-face sessions, in-person and remotely supervised sessions will be videotaped with participants' consent. Two post-doctoral fellows, who will be independent of the team will review the recorded videos and complete a performance checklist. The collected data will be used to evaluate the feasibility of the intervention.

Outcome evaluation

The following measuring tools/methods will be used for outcome evaluation at baseline (T0), immediate post-intervention (T1), and 3 months post-intervention (T2). Physical performance will be the primary outcome, while the rest will be the secondary outcomes.

Physical performance: The Short Physical Performance Battery[31] will be used to assess physical performance and is well validated and widely adopted in clinical and research settings. It is a brief performance-based assessment consisting of 3 timed-tasks, including standing balance, walking speed, and chair stand tests. The timed results will be rescaled to obtain a score ranging from 0 to 12, higher scores indicate better physical performance.

Muscle mass and strength: The appendicular skeletal muscle mass (ASM) will be measured with the bioelectrical impedance analysis (In-Body). This is one of the gold-standard evaluation tools suggested by international guidelines for assessment of muscle mass. It is widely used in research and hospital setting for clients with sarcopenia. The muscle strength will be measured with a hydraulic dynamometer (Jamar). The standard protocol suggested by international guidelines will be followed, the maximum reading of at least 2 trials using the dominant hand in a maximum-effort isometric contraction will be recorded.

Cardiac-specific functional status: The Seattle Angina Questionnaire will be used to measure cardiac-related functional status. It has 19 items in 5 subscales: physical limitation, angina stability, angina frequency, treatment satisfaction and disease perception.[32] It is scored on a 1–5 or 6 sequentially coded scale and subscale scores are transformed to a scale of 0–100, with higher scores indicating higher levels of functioning and fewer limitations. The Chinese version has been shown to be reliable, valid, and sensitive to clinical change.[32]

Cardiac-specific HRQoL: The MacNew will be used to measure cardiac-specific HRQoL.[33] It has 27 items scored on a 1-7 scale, and then global score is calculated by summing the item scores, with higher scores representing better HRQoL. MacNew has good internal consistency, test-retest reliability, concurrent and discriminant validity.[33]

Psychological distress: The Patient Health Questionnaire-4 (PHQ-4)[34] will be used to measure psychological distress. It consists of 4 items assessing anxiety and depression, to be responded on a 4-point Likert scale. The composite total score ranges from 0 to 12, higher scores indicate greater level of anxiety and depression. It has good psychometric properties.[34]

MACCE and hospital readmission rates: will be monitored from enrollment to the study to 3 months after the intervention through record review.

Data collection procedure and randomization

Ethical approval will be obtained from the institutional review board. Active recruitment strategies will be used by posting recruitment notes on the newsletters and Facebook of the

Care For Your Heart, and posters in the center. A research assistant will screen the eligibility of the potential participants at the center of Care for Your Heart by measuring the calf circumference to identify patients with possible sarcopenia. A non-elastic measuring tape will be used to measure both calves, those individuals with the maximum value meeting the guideline-specified cut-offs (<34 cm in male; <33 cm in female) will be invited to undergo a more in-depth evaluation according to the eligibility criteria of this study. All eligible patients will be invited to participate. After obtaining the written informed consent, the research assistant will collect the baseline data (T0), then he/she will randomly assign participants into the intervention or control group with block randomization to ensure even distribution of participants in the two study groups over the study period. Patients will be allocated chronologically in a 1:1 ratio by using a computer-generated random sequence to determine the block size (4, 6 and 8) and respective study group allocation. The group allocation will be determined according to the random sequence codes placed in sealed opaque envelopes. Participants in the intervention group will receive the strength-building intervention whereas the control group will receive usual care. To minimize biases, another independent research assistant who is blinded to the group allocation will be responsible for collecting post-intervention data at another two time points (T1 and T2) in the center of the Care For Your Heart. Each assessment will last for approximately 30 minutes.

Data analysis

Statistical analysis of the outcome comparisons will be performed on the basis of the intention-to-treat principle. Descriptive statistics will be used to describe the characteristics of the sample, the feasibility of, acceptance, and compliance with the intervention. The baseline characteristics will be compared between the study groups using a t-test, chi-square test or Fisher's exact test where appropriate. Repeated measure ANOVA will be used to determine the effects of the intervention by comparing differential between group changes across the 3 time-points. All statistical analyses will performed using IBM SPSS 27.0. All statistical tests will be two-sided, and a p-value of less than 0.05 will be considered statistical significant. Content analysis will be used to analyze the qualitative data. These data will be used to optimize the intervention design and feasibility for the full scale randomized controlled trial.

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