

# Effect of voluntary breathing exercises on stable coronary artery disease in heart rate variability and rate-pressure product: a study protocol for a single blind, prospective randomized controlled trial

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## Study protocol

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# Abstract

**Background:** At present, China has more than 11 million patients with stable coronary heart disease, becoming a major public health problem. The pathological changes of coronary heart disease can lead to dysfunction of cardiac autonomic nervous system, which increases the risk of complications such as malignant arrhythmia (ventricular flutter, ventricular fibrillation, etc.), heart rate, systolic blood pressure, and rate-pressure-product (RPP), which is highly correlated with myocardial oxygen consumption and indirectly reflects myocardial blood supply and oxygen consumption. Although the guidelines recommend that such patients take drugs to reduce heart rate and myocardial oxygen consumption, the clinical control of heart rate is still not ideal. Thus, in this trial, we will use voluntary breathing exercises as the strategy of exercise rehabilitation patients with SCAD, in order to increase the vagus nerve activity and/or reduce the sympathetic nervous activity, help maintain or rebuild the balance of plant nerve system, improve the time domain index of heart rate variability, reduce the burden on the heart, relieve patients' anxiety and other negative emotions. **Methods:** This is a 6 months single-blind, randomized controlled clinical trial that will be conducted in the First Affiliated Hospital of Soochow University. Eighty patients who fill out the Informed Consent Form are registered and randomized 1:1 into the VBE-based clinical trial monitoring group (n = 40) or the Routine follow-up group (n = 40). The VBE-based clinical trial monitoring group is given VBE training on the basis of conventional treatment and health education, while the control group received conventional health education and follow-up. The primary outcome will be measured heart rate variability (HRV) and rate-pressure product (RPP). Secondary outcomes will include changes in self-rating anxiety scale (SAS), total cholesterol(TC), triglyceride (TG), high density lipoprotein (HDL-C), low density lipoprotein(LDL-C), weight and body mass index (BMI). **Discussion:** This trial will carry out scientific respiratory exercise for patients with stable coronary heart disease, which belongs to the category of active secondary prevention for patients, and changes from remedial to pre-protective. VBE is easy to operate, and is not limited by time and place. It is very important and meaningful to carry out VBE for patients with SCAD. This study will provide considerable evidence for further large-scale trials and alternative strategies for the rehabilitation nursing of patients with SCAD. **Trial registration:** This study is registered at Chinese Clinical Trials Registry.gov, ID:1900024043. Registered on 23 June 2019.

## Background

Stable coronary artery disease (SCAD) is one of the most common types of coronary artery disease. It is characterized by chronic delay and high recurrence. Several studies[1–3] have demonstrated that pathological changes of coronary heart disease can lead to dysfunction of cardiac autonomic nervous system, which is manifested as hyperactivity of sympathetic nerve and decreased excitability of vagus nerve. Thayer JF et al.[4] concluded that autonomic nervous dysfunction leads to cardiac dysfunction and cardiovascular disease. They are also at an increased risk of complications such as malignant arrhythmia (ventricular flutter, ventricular fibrillation, etc.), increased heart rate, increased systolic blood pressure, and increased rate-pressure-product (RPP), which is highly correlated with myocardial oxygen consumption and indirectly reflects myocardial blood supply and oxygen consumption[5], and is earlier

than the change of ECG. As a consequence, it is of utmost importance to no longer neglect stability of autonomic nervous function during rehabilitation on stable coronary artery disease.

Heart rate variability(HRV) is recognized as a new non-invasive quantitative evaluation method of autonomic nervous system function developed in recent years[6]. HRV refers to the small difference between cardiac cycles, which reflects the sympathetic and vagus nervous systems regulating the balance state of the cardiovascular system[7]. It was shown to be related to subtle time changes and patterns of each cardiac cycle, while the average heart rate can only appear normal or abnormal. Shen Yan-fang et al.[8] analyzed the results of 24-hour dynamic electrocardiogram of 156 patients with coronary heart disease and found that heart rate variability decreased, ejection fraction decreased, and the incidence of cardiovascular events increased.

The research on the effect of respiration on HRV has become a hot topic in recent years [9–10]. Previous studies have demonstrated that respiration is one of important influencing factors for HRV[11,12]. Cicek S et al.[13] confirmed that deep and slow breathing can make people turn from depression to relaxation, and improve the regulation function of human organs or autonomic nerves, so as to improve the adaptability of human body. Voluntary breathing exercises (VBE) refers to a treatment or rehabilitation method for adjusting breathing behaviors by trainees according to certain breathing patterns (frequency, depth, ratio of expiratory/inspiratory time, chest/belly style) without the use of auxiliary equipment or equipment[14]. Initially, VBE was applied in the prevention and treatment of chronic obstructive pulmonary disease[15], chest surgery[16] and other diseases related to respiratory system. Subsequently, it gradually spread to the treatment of other chronic diseases such as endocrine and nervous systems[17,18]. Some authors consider that VBE effectively improved quality of life, reduced symptoms associated with a variety of anxiety and depression[19,20]. VBE is also applied to treat cardiovascular complaints, such as primary hypertension[10,15], heart failure[18,21,22], arrhythmia[23], and so on. Kawecka-Jaszcz K et al. [22] found that respiratory exercise combined with exercise rehabilitation for a period of 10 to 12 week in patients with chronic heart failure had a better effect on ejection fraction and 6-minute walk test, but this study failed to observe the functional changes of autonomic nervous function. Westerdahl E et al.[24] showed that 2-week respiratory exercise reduced systolic blood pressure in CHD patients, but had no effect on heart rate and diastolic blood pressure, which may be closely related to the short intervention time. Study on the efficacy of VBE by Huang Hui et al.[25] also reported significant reductions in heart rate and systolic blood pressure, and there were no effects on diastolic blood pressure. The meta-analysis results of independent breathing exercise conducted by the research team in the previous stage showed that[26](6 RCT articles, all in English), VBE had significant effects on improving resting heart rate, systolic blood pressure and diastolic blood pressure in patients with coronary heart disease.

However, more research is necessary regarding the effect of VBE on stable coronary artery disease. In 2014, the American college of cardiology (ACC) and the American heart association (AHA)[27] pointed out that drug therapy and lifestyle intervention are key to controlling or delaying the stable progression of coronary heart disease, reducing complications, disability rate and mortality rate. As one of the ways of life behavior intervention, VBE has become a new way of comprehensive intervention for coronary heart

disease. To date, there are no definite data on the effect of VBE in patients with SCAD, particularly in the Chinese population. Thus, we present the protocol of a single blind, randomized controlled trial to investigate the effects of VBE on SCAD. We hypothesize that VBE is effective for the management of secondary prevention of coronary heart disease.

### *Research hypothesis*

On the basis of [routine rehabilitation](#) guidance, VBE will as an aid in the strategy of exercise rehabilitation patients with stable coronary heart disease, in order to increase the vagus nerve activity and/or reduce the sympathetic nervous activity, help maintain or rebuild the balance of plant nerve system, improve the time domain index of heart rate variability in patients with SCAD, reduce the burden on the heart, relieve patients' anxiety and other negative emotions in this study (Figure 1).

### *Objectives*

The main goal of this randomized controlled trial is to evaluate the effect of VBE on heart rate variability and myocardial oxygen consumption in patients with stable coronary heart disease. Primarily, HRV will be measured using the generally recommended time-domain analysis in 24-hour; secondarily, since rate-pressure-product are highly correlated with oxygen consumption of myocardium, it will be used as an indicator to estimate oxygen consumption of myocardium.

The second objective is to explore the effect of VBE on reducing anxiety in patients with SCAD. Anxiety will be measured using the Self-rating Anxiety Scale(SAS) developed by Zung[28] in 1971.

## **Methods**

### *Study design and setting*

This is a 6 months single-blind, randomized controlled clinical trial that will be conducted in the First Affiliated Hospital of Soochow University. Eighty patients who fill out the Informed Consent Form are registered and randomized 1:1 into the VBE-based clinical trial monitoring group (n = 40) or the Routine follow-up group (n = 40). The VBE-based clinical trial monitoring group is given VBE training on the basis of conventional treatment and health education, while the control group received conventional health education and follow-up. The two groups will be followed up for three months (The first step).

Considering the ethics and the fairness of the resources, we refer to the step-wedge design[29] and give the control group the same VBE guidance and follow up for another three months (The second step) ((see the flow diagram in Figure 2). The cardiovascular medicine department of the First Affiliated Hospital of Soochow University is currently the largest cardiovascular disease diagnosis and treatment center in South Jiangsu Province, China. The department carried out the first PTCA surgery in China in 1983. It has 180 beds, including 20 CCU beds with complete equipment, 4 cardiac catheterization rooms with advanced equipment, as well as cardiac supersonic room and cardiac function room, and 1500m<sup>2</sup>

cardiovascular laboratory. Annually, an average 100,000 outpatients, 5000 open-heart surgery candidates and 400 emergency operations are treated in the department.

### *Sample size*

The sample size estimation was carried out using the formula for comparison of mean values of two independent samples[30]:  $n_1 = n_2 = 2 * [(Z_{\alpha} + Z_{\beta}) * \sigma / \delta]^2 + Z_{\alpha}^2 / 4$ . According to the method proposed by Chen J et al.[31],  $\sigma$  is the standard deviation of a research index.  $\delta$  is the difference between the average of the two population indexes.  $N_1$  and  $n_2$  were two samples required content respectively  $\alpha$  error probability of  $\alpha$  and  $\beta$  error probability of  $\beta$  of the z value. At bilateral  $\alpha = 0.05$ ,  $P = 0.8$ ,  $Z_{\alpha/2} = 1.96$ ,  $Z_{\beta} = 0.842$ ,  $\sigma = 12.68$ ,  $\delta = 10.39$ , a sample size of 25 subjects per group was required. With an estimated 20% dropout, the final sample size of 40 was determined (a total of 80 subjects, 40 in each group).

### *Participants*

#### *Inclusion Criteria*

Patients will have to meet the following eligibility criteria to be included in the study:

1. Patients aged 45–75 years
2. Meeting the diagnostic criteria of SCAD formulated by t by the interventional cardiology group of the cardiovascular disease branch of the Chinese medical association, the atherosclerosis and coronary heart disease group, and the professional committee for the prevention and treatment of thrombosis of the cardiovascular physicians branch of the Chinese medical association[32]
3. Heart rate > 60 beats/min[33]
4. Living in Suzhou for at least six months from the start of the trial
5. Those who are sane, rational, and able to communicate verbally
6. Those who agree to participate and provide written informed consent

#### *Exclusion Criteria*

Patients will be excluded from the study if:

1. Revascularization has been carried out or conducted in follow-up
2. Combined arrhythmia that shows on an electrocardiogram (ECG)
3. Any self-reported respiratory disorder
4. Severe liver and kidney diseases
5. Diagnosed with hypothyroidism or currently taking thyroid medications
6. Diagnosed with moderate or below anemia (hemoglobin (Hgb) level less than 9g/dL)
7. With any mental disorders(for example, major depressive disorder, anxiety disorder, substance use, etc.) in the past 12 months

8. Pregnancy, and practicing yoga/meditation/relaxation/mindfulness on a regular basis
9. Other reasons determined by the investigators that make participation in the clinical trial inappropriate

#### *Withdrawal criteria*

Participants who meet the criteria summarized below are withdrawn from the study. The subjects who are withdrawn after randomization will be followed up for outcomes. Reasons for withdrawal will be documented in follow-up records and data will be analyzed using the intention-to-treat (ITT) principle[34].

1. Fail to exercise for 2 weeks in a row
2. Three consecutive telephone connections failed during the follow-up period
3. Patients who quit due to various reasons

#### *Randomization*

Eligible participants who will provide written consent to participate in this clinical trial will be randomly assigned to a treatment group or a control group with an allocation ratio of 1:1. Random sequencing will be generated by an independent professional statistician using the EXCEL to generate 80 random Numbers. The serial numbers assigned to each patient are kept in an opaque, sealed envelope. All the participants will be asked to pick one sealed envelope and pass it onto the research study team member. The participants will be randomly assigned to two groups. Each group will have 40 individuals.

#### *Blinding*

The research study team member who enters information about a participant's eligibility is the only person to know the participants' allocation until the participant has completed the entire protocol. The research team member who involved in subjective efficacy assessments is blinded to the participant's group allocation to receive VBE or conventional treatment. Participants are similarly blinded to their own group allocation, and they will be cautioned not to remark on the VBE exercises that they receive to the research study team member performing the outcome measures. Results from the outcome measures will not be revealed to the participants until after all recruitment, treatment and assessments have been performed for all 80 participants.

#### *Procedures*

#### *Study schedule*

The items to be measured at each visit are presented in Table 1.

#### *Baseline assessment*

After the screening visit, if a participant fulfills inclusion criteria and has signed the informed consent form, he will be assigned to the baseline assessment. The baseline assessment takes place at visit 1. Baseline assessment includes patients' basic information (such as age, gender, marriage, occupation, education level, dietary habit, income, family history, comorbidity, etc.), physical anthropometry indexes (height, body weight, blood pressure, heart rate, body mass index, RPP, and HRV), testing items (triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein, and fasting plasma glucose), questionnaires (Self-rating Anxiety Scale (SAS)).

### *Intervention group*

After enrollment, the intervention group was given the following measures on the basis of receiving the routine health education. Each patient in the intervention group will be assigned a health management document and have a follow-up timetable.

1. Development and distribution of manuals: Chinese biomedical literature database (CBM) will be searched by Chinese search terms "health management, diet, exercise, heart rate and blood pressure", and Cochrane Library, JBI and Medline will be searched by corresponding English search terms. After two rounds of expert consultation, the health education manual for patients with SCAD will be constructed and distributed to each patient in the intervention group upon discharge.
2. One-to-one telephone follow-up or home visit: The patient will be followed up after discharge. Follow-up time is 3 months for a total of 12 weeks (once a week in the first month and once a month after that until 3 months). Two follow-up methods will be adopted: telephone and home visit. The telephone follow-up is about 5–10 minutes each time. Holding time could be extended if there is any problem consultation. Home visits will be scheduled with patients in advance, and about 30–60 minutes each time. During the follow-up, we will address the patient's doubts and evaluate the effectiveness of the intervention.
3. VBE guidance: Before VBE, patients should rest for 5min and then do it in a well-ventilated room with appropriate temperature. The researchers help patients take comfortable positions (supine, repose and standing are all acceptable, sitting is recommended), straighten their head and back, and relax their whole body. The researchers instruct patients to extend the duration of exhalation and inhalation, and to minimize the breathing rate to 6 breaths per minute. Participants practice silently counting from 1001–1004 on the inhale phase and 1001–1006 on the exhale phase to control the breathing rhythm and slow down the frequency. Participants are also encouraged to use abdominal breathing (a bulge in the abdomen when inhaling and a depression when exhaling) to deepen breathing depth and reduce breathing rate. Practice time: The total time per day is more than 30min[25], which can be delivered in batches, but at least 10 minutes at a time and at least 5 times a week[12]. Attention: The participants should breathe in and out of the nose during the whole process. The intensity of the exercise should not cause breath-holding or any physical discomfort. If discomfort occurs, participants may rest for a while and continue the exercise if no discomfort is present. For the first three days of the study, participants are asked to complete exercises in an

outpatient classroom and the researchers will assess whether the exercises are correct to correct wrong breathing patterns.

4. Exercise log: Each participant is given an exercise log and asked to record the number and time of exercise every day.
5. Network support: The research group will make self-breathing exercise courseware or video and transmit it to each participant through the network, so that participants could browse at any time.

### *Control group*

1. Routine education: On the first day after enrollment, researchers explain relevant knowledge of SCAD to patients, including risk factors, diet, weight control, physical exercise, blood pressure and lipid management, etc.
2. Telephone follow-up: 1 time per month to 3 months, each time about 5–10 minutes, receiving telephone counseling from patients.
3. Post-intervention: The control group will be given the same intervention measures 3 months later, and the effects of the control group will be compared between prior to and after the intervention.

### *Outcome*

#### *Primary outcome measure*

The change in the HRV and RPP will be used as the primary outcome measure. The mean difference between the change scores of the two groups will be calculated.

1. Heart rate variability (HRV): Currently, 24-hour time domain analysis index is generally recommended for HRV detection[35]. All patients will be tested by 12-channel dynamic electrocardiograph (TLC5000) to detect the time domain index of heart rate variability between visit 1 (baseline) and visit 8 (after treatment). During the examination, participants are required to have adequate sleep overnight, maintain a quiet and peaceful environment, avoid too intense exercise, changes in posture and mood swings, avoid drinking stimulating drinks such as coffee, and try not to take drugs that may interfere with autonomic nerves. Indicators include: (1) Standard deviation of normal to normal (SDNN), SDNN is the standard deviation of 24h continuous RR interval; (2) Standard deviation of average 5min n-n intervals (SDANN), SDANN is the standard deviation of the mean of continuous RR intervals every 5min for 24h; (3) Square root of the mean squared differences of successive NN intervals (RMSSD), RMSSD is the root mean square of all RR intervals within 24h; (4) Percent of the number whose difference between adjacent NN interval are more than 50ms (PNN50), PNN50 is the percentage of sinus beats in which the difference between the two adjacent normal RR stages was greater than 50ms at 24h; (5) Mean of standard deviations of normal-to-normal intervals for each 5-min period (SDNNindex), SDNNindex is the mean of the SDs for 5 min segments. All dynamic electrocardiograms are completed by professionals in the electrocardiogram room of the same

hospital, and HRV time domain indexes are automatically analyzed and calculated by the electronic computer.

2. Rate-Pressure Product (RPP): RPP is used to estimate myocardial oxygen consumption[36]. The normal value of RPP is <12000, and the smaller the product is, the more stable the patient's condition is. In this study, electronic blood pressure monitor (OMRON, HEM-4011C) will be used to measure patients' heart rate and blood pressure at visits 1, 4,7 and 8. The measurement time is scheduled to be from 2 PM to 3 PM, and the room temperature is maintained at about 25°C in the same outpatient classroom. After sitting for 15 minutes, the patient will be measured at the right elbow. Ensure that each patient do not eat or drink strong tea, coffee or other stimulating drinks 1h before the measurement.

### *Secondary outcome measure*

1. Self-rating Anxiety Scale (SAS): The Zung Self-Rating Anxiety Scale (SAS) is an anxiety measure designed by William WK Zung in 1971 to quantify the level of anxiety for patients experiencing anxiety related symptoms[28]. The SAS test is self-administered, with each response using a 4-point scale, from 'none of the time' to "most of the time." There are 20 questions with 15 increasing anxiety level questions and 5 decreasing anxiety questions. According to SAS standard scores, the respondents are divided into four categories: no anxiety symptoms (less than 50 points), mild anxiety (50–59 points), moderate anxiety (60–69 points) and severe anxiety (70 points and above).The scale has been widely used in China and its validity and reliability have been verified.
2. Metabolic profile: total cholesterol(TC),triglyceride(TG), high density lipoprotein (HDL-C) and low density lipoprotein(LDL-C).
3. Body composition: weight, body mass index (BMI).

### *Safety outcome measure*

The safety assessment will be performed for the participants who have been received VBE training more than once. The subjects' vital signs and general physical status will be examined at every visit. The occurrence of adverse event (AE) will be checked at visits 3,4,5,6,7, and 8.The investigators should educate the subjects to report any AE that occurs after training. All adverse events that occur after the start of this trial should be documented in the case report form whether or not they are related to VBE. All AEs will be evaluated for causal relationships.

### *Statistical analysis*

The Kolmogorov-Smirnov test and p-p diagram analysis will be used to test the normal distribution of continuous variables. Continuous variables will be presented by mean±standard deviation if they are normally distributed. Mann-whitney U test will be used and expressed by median with interquartile range if they are not normally distributed. Chi-square or Fisher's exact tests will be used for comparison of dichotomous data. Both per protocol (PP) analysis and intention-to-treat analysis (ITT) will be used to

determine the robustness of the evidence. An independent statistics expert will perform the statistical analysis in a blind manner. All statistical analyses of the data will be performed by using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA).

## Discussion

Heart rate variability (HRV) is currently recognized as one of the indicators reflecting impaired autonomic nervous function[37], which is affected by sympathetic and parasympathetic nerves and shows fluctuations. Studies have shown that[38] myocardial ischemia caused by coronary heart disease promotes a long-term high level of sympathetic nerve activity, changes the normal balance between sympathetic and vagus nerves, and shows a decrease in HRV on the dynamic electrocardiogram. Ferrari R et al.[39] found that multiple time-domain and frequency-domain indexes of HRV in patients with coronary heart disease were significantly reduced, and autonomic nerve function was impaired to varying degrees. SDNN, HRV's time domain index, reflects the overall level of heart rate variation; SDANN mainly reflects sympathetic tension; SDNNindex is affected by vagus tension and variable sensory tension; RMSSD mainly reflects vagus tension, and PNN50 variation trend is basically the same as RMSSD[40]. The high-frequency components of HRV, also known as "respiratory components", synchronize with respiratory movements and regulate heart rate variability through central mechanism and mechanical influence. Therefore, in recent years, scholars have focused on the effect of respiration on HRV[41]. Rossi Caruso et al.[42] conducted intervention on 10 male patients with heart failure and 10 healthy patients, respectively measuring heart rate and RR interval during and after lying down, sitting down, walking, breathing training, and found that deep breathing training could improve heart rate variability in patients with chronic heart failure.

China 2018 guidelines for diagnosis and treatment of stable coronary heart disease[32] pointed out that the heart rate should be controlled at 55–60 times /min during the treatment of SCAD to reduce myocardial oxygen consumption, and recommended that patients with SCAD should use beta blockers as early as possible to slow down the heart rate and reduce myocardial contraction. Thus, heart rate control is one of the most important measures in secondary prevention of coronary heart disease. However, even if such patients take drugs regularly in China, the heart rate still cannot reach the target rate, and only 35.9% patients reach the HR standard [43]. Multiple studies have shown that increased heart rate can induce the occurrence of cardiovascular diseases, especially cardiovascular events[44,45]. Framingham followed up 5209 male patients for 36 years, and the results showed that the all-cause mortality of cardiovascular diseases including coronary heart disease gradually increased with the increase of heart rate[46]. The research results of Jae SY et al. [47] showed that rapid heart rate was likely to cause malignant ventricular arrhythmia, which was related to long-term coronary artery calcification.

VBE includes controlled deep breathing, lip contraction breathing and abdominal breathing[26]. VBE can effectively interfere with autonomic nerve function, and can be reversely adjusted according to the characteristics of autonomic nerve function under different pathological conditions. If the basic state is characterized by excessive excitability of sympathetic nerve, its excitability can be reduced, but if the

vagus nerve activity is low, it can increase its activity, etc., so as to have a corresponding impact on BP and HR[48]. Deep and slow mode VBE can increase parasympathetic activity, reduce sympathetic activity and improve cardiovascular function [26]. VBE is not limited by time, place, auxiliary equipment, etc., which is one of the methods of lifestyle intervention. VBE is one of the frequently used alternative strategies for rehabilitation exercise of patients with cardiovascular diseases, which can be a new approach for comprehensive intervention of coronary heart disease[7,11].

Our trial has several strengths. Firstly, the purpose of this study is to explore the effects of VBE on HRV and RPP in patients with SCAD. There have been studies on the application of VBE in clinical fields at home and abroad, and our research team studied the effect of VEB of one month on heart rate and blood pressure of patients after PCI in the early stage, achieving good results. Therefore, we have a solid foundation and stable research direction. Secondly, the study through health education guidance and breathing exercise intervention, fully arouses the awareness of self-management of coronary heart disease patients, explores more practical and effective methods of rehabilitation and exercise for patients, improves patients' active participation consciousness and enthusiasm of disease treatment, and provides basis for the implementation of rehabilitation and exercise methods for clinical medical staff and patients. **Thirdly**, this study explores the effect of VBE on HRV of patients with SCAD, which is a secondary prevention of cardiovascular and cerebrovascular diseases, which has not been involved in China.

However, there are a few limitations of this study. The first is due to limited funds, the study is conducted only in Suzhou. Second, the implementation of VBE is carried out in the patient's family. Although self-monitoring records will be issued to each patient, the possibility of random recording may occur, and the researchers cannot objectively quantify the compliance of patients with VBE. **In addition**, this study cannot avoid the influence of drug adjustment on HR and BP during the intervention period. Therefore, we will compare the medication status of the two groups when collecting baseline data.

After completion of this study we will carry out large-sample, multi-center and high-quality RCT in future studies to further verify the role of the implementation of VBE in the maintenance and promotion of health and provide reliable evidence-based evidence for the promotion and application of VBE in clinical practice. This protocol was written according to the SPIRIT 2013 Statement[49]. The SPIRIT Checklist can be found as an additional file (see Additional file 1).

### *Trial status*

Protocol version number and date: version 1.0, 1 March 2019. The study was registered at Chinese Clinical Trials [Registry.gov](http://www.chictr.org) on 23 June 2019. Recruitment was started on 1 June 2019 and is expected to end in **December** 2020. So far, 16 patients have been recruited for this trial.

## **Abbreviations**

SCAD:Stable coronary artery disease;ECG:Electrocardiography;HRV:Heart rate variability;RPP:Rate-pressure-product;VBE:Voluntary breathing exercises;RCT:Randomized controlled trial;ACC:American college of cardiology;AHA:American heart association;SAS:Self-rating Anxiety Scale;CCU:Coronary care unit;Hgb:Hemoglobin;CBM:Chinese biomedical literature database;SDNN:Standard deviation of normal to normal;SDANN:Standard deviation of average 5min n-n intervals;RMSSD:Square root of the mean squared differences of successive NN intervals;PNN50:Percent of the number whose difference between adjacent NN interval are more than 50ms;SDNNindex:Mean of standard deviations of normal-to-normal intervals for each 5-min period;TC:Total cholesterol;TG:Triglyceride;HDL-C:High density lipoprotein;LDL-C:Low density lipoprotein;BMI:Body mass index;AE:Adverse event;PP:Per protocol;ITT:Intention-to-treat analysis.

## Declarations

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### *Availability of data and materials*

Not applicable.

### *Authors' contributions*

YYH and QW have written the first manuscript for this trial. QZ and XHW contributed to the funding and the design of the study. LL, XJ and ZSH designed the study, coordinated to acquire the data, and helped to draft the manuscript. YYH, QW, and ZXT calculated the sample size and determined the methods of statistical analysis. LL and QW will monitor this trial. LL, QW, XJ, YYH, ZSH, and ZXT participated in the design of the study. QSL, WQ, LL, WZ, JML, YYH, and YX coordinated to acquire the data. QZ and XHW critically revised the manuscript. All authors read and approved the manuscript.

### *Competing interests*

The authors declare that they have no competing interests.

### *Consent for publication*

Not applicable.

### *Ethics approval and consent to participate*

This study had been approved by the ethics committee of the First Affiliated Hospital of Soochow University (Reference: 2019037), and conforms to the principles of the Helsinki declaration. The present trial is registered at <http://www.chictr.org.cn/index.aspx> (ChiCTR 1900024043). All participants signed the informed consent form prior to participation.

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### *Additional files*

*Additional file 1*: SPIRIT 2013 checklist:recommended items to address in a clinical trial protocol and related documents. (DOCX 121 kb)

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## Tables

**Table 1 Schedule of enrollment, intervention, and assessment**

	Screening	Post allocation						Close-out
	Visit 1 (day – 5 to – 2)	Visit 2 (day 0)	Visit 3 (week 1)	Visit 4 (week 2)	Visit 5 (week 3)	Visit 6 (week 4)	Visit 7 (week 8)	Visit 8 (week 12)
Informed consent	X							
Inclusion/exclusion criteria	X							
Randomization		X						
Intervention		X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X
Body measurement <sup>a</sup>	X	X	X	X	X	X	X	X
Demographic, sociological information <sup>b</sup>	X							
Medical history <sup>c</sup>	X							
General physical examination	X							X
HRV	X							X
RPP	X			X			X	X
Self-rating Anxiety Scale	X							X
Laboratory tests <sup>d</sup>	X			X				X
Adverse event monitoring			X	X	X	X	X	X

<sup>a</sup> Height and weight, but only weight for visit 2 and follow-up

<sup>b</sup> Age job, education level, dietary habit, smoking habit, drinking habit, etc.

<sup>c</sup> Including general medical history and family history of coronary heart disease

<sup>d</sup> Including triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein, and fasting plasma glucose

## Figures

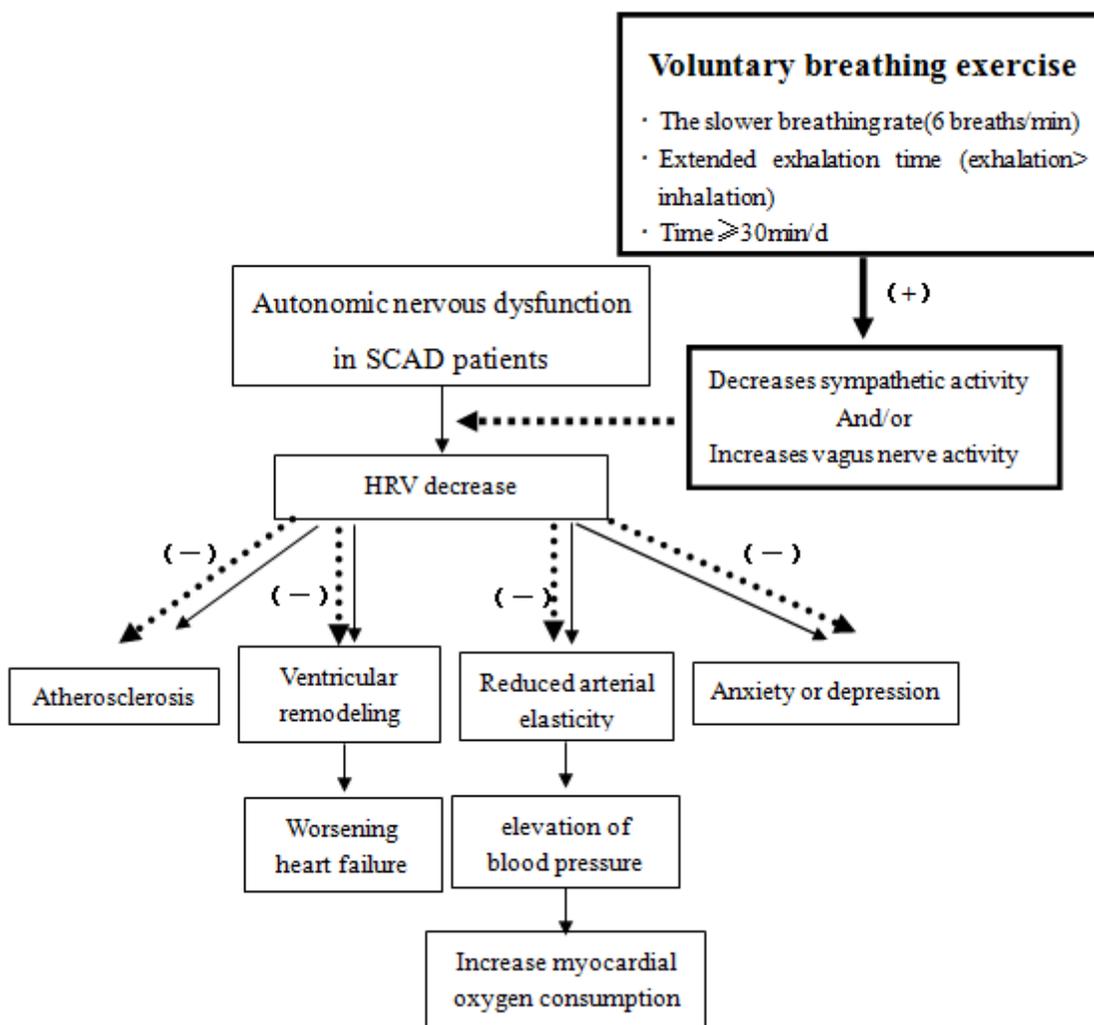


Figure 1

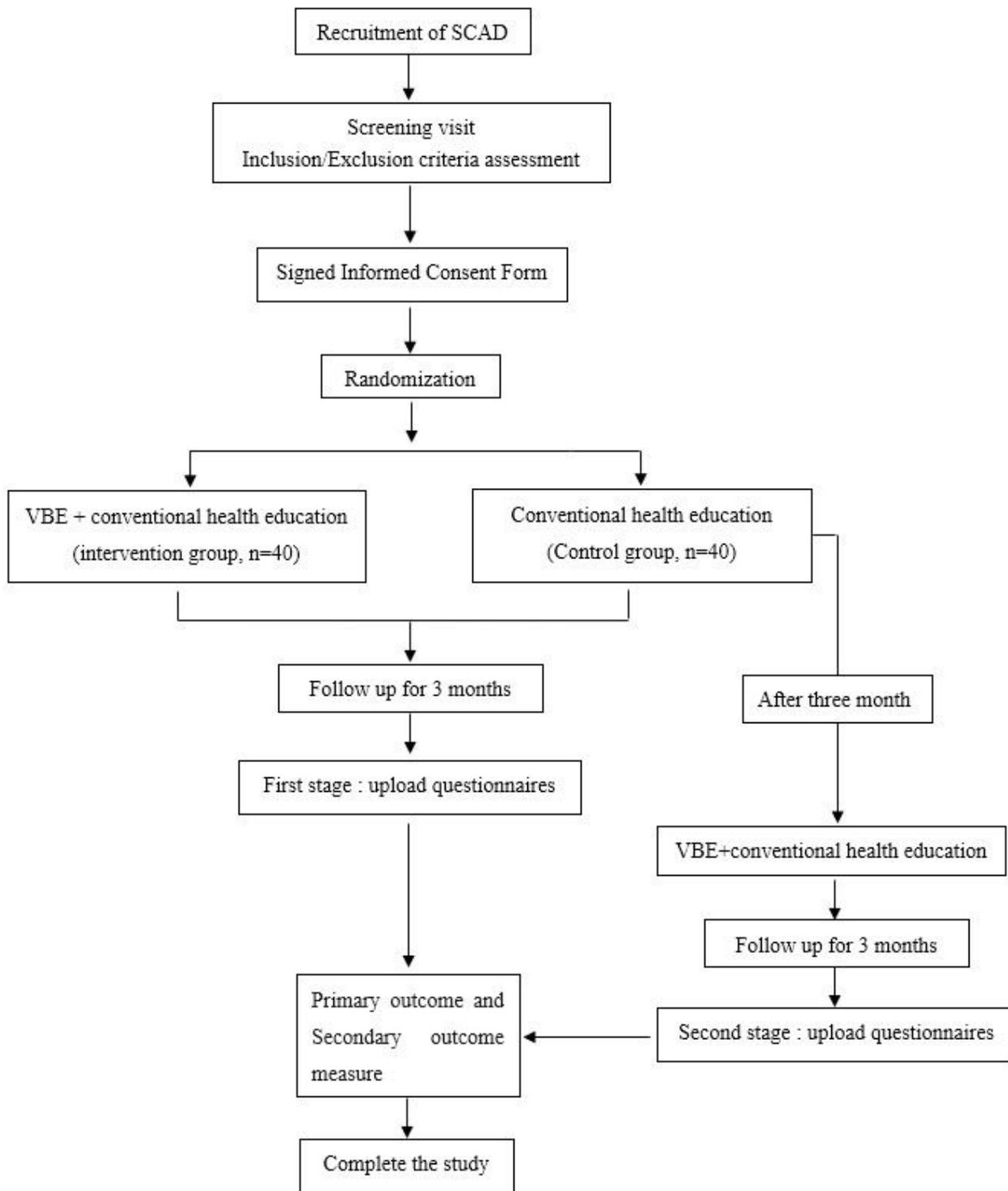


Figure 2

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