Efficacy of Yuxintong capsule on cardiorespiratory fitness in patients with stable coronary heart disease: A multicentre, randomized, double-blind, placebo-controlled, parallel-group clinical trial

愈心痛胶囊对稳定型冠心病患者心肺耐力的疗效：一项多中心、随机、双盲、安慰剂对照、平行组临床试验

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Abstract

摘要

Ethnopharmacological relevance: Yuxintong capsule, a traditional Chinese patent medicine, has been widely used in the treatment of coronary heart disease (CHD). However, whether it can improve cardiopulmonary fitness (CRF) in patients with CHD remains unclear.

民族药理学相关性：愈心痛胶囊是一种传统中成药，已广泛用于治疗冠心病。然而，它是否能改善冠心病患者的心肺功能尚不清楚。

Aim of the study: To evaluate the efficacy and safety of Yuxintong capsule in CRF in patients with stable CHD.

研究目的：评估愈心痛胶囊对稳定型冠心病患者心肺耐力的疗效和安全性。

Materials and methods: A multicentre, randomized, double-blind, placebo-controlled, parallel-group trial was conducted in 13 hospitals in China from March 2021 to November 2021, and 404 patients with stable CHD were randomly assigned to receive either Yuxintong capsule

and conventional Western medicine (Yuxintong group) or placebo and conventional Western medicine (placebo group) in a 1:1 ratio for 12 weeks (ChiCTR2000041293, December 23, 2020). The primary outcomes were peak oxygen uptake (VO2peak) and anaerobic threshold (AT). The secondary outcomes were metabolic equivalents (METs), duration and onset time of 1-mm ST-segment depression on electrocardiography (ECG), and 36-Item Short Form Health Survey (SF-36) scores. The main safety indicators included complete blood count, urinalysis, liver function, renal function, coagulation function, and 12-lead electrocardiogram. And adverse events were recorded throughout the trial.

材料与方法：2021 年 3 月至 2021 年 11 月，在中国 13 家医院开展了一项多中心、随机、双盲、安慰剂对照、平行组试验，404 例稳定型冠心病患者按 1:1 比例随机分配接受愈心痛胶囊联合常规西药治疗（愈心痛组）或安慰剂联合常规西药治疗（安慰剂组），疗程 12 周（ChiCTR2000041293，2020 年 12 月 23 日）。主要终点为峰值摄氧量（VO2peak）和无氧阈（AT）。次要终点为代谢当量（METs）、心电图（ECG）上 1mm ST 段压低的持续时间和发生时间，以及 36 项健康调查简表（SF-36）评分。主要安全性指标包括血常规、尿常规、肝功能、肾功能、凝血功能和 12 导联心电图。在整个试验过程中记录不良事件。

Results: 369 patients, 187 in the Yuxintong group and 182 in the placebo group, were finally included for analysis. Compared with placebo group, 12-week treatment with Yuxintong showed an improvement in AT (0.98 ± 2.88 vs. 0.12 ± 2.79 $mL \cdot kg^{-1} \cdot min^{-1}$; LSMD, 0.80 [95% CI: 0.28 to 1.32]; $P < 0.025$), and general health (13.61 ± 15.13 vs. 8.29 ± 14.14; LSMD 5.30, [95% CI: 2.33 to 8.31]; $P < 0.05$) and vitality scores (12.46 ± 11.32 vs. 6.01 ± 11.41; LSMD 6.43, [95% CI: 4.13 to 8.31]; $P < 0.05$) on SF-36 scale. The other outcomes did not significantly differ between the two groups. The adverse events were similar between the two groups.

结果：最终纳入分析 369 例患者，其中愈心痛组 187 例，安慰剂组 182 例。与安慰剂组相比，愈心痛治疗 12 周后 AT 改善（0.98 ± 2.88 vs. 0.12 ± 2.79 $mL \cdot kg^{-1} \cdot min^{-1}$；LSMD 0.80 [95% CI: 0.28~1.32]；$P < 0.025$），SF-36 量表中总体健康（13.61 ± 15.13 vs. 8.29 ± 14.14；LSMD 5.30 [95% CI: 2.33~8.31]；$P < 0.05$）和活力评分（12.46 ± 11.32 vs. 6.01 ± 11.41；LSMD 6.43 [95% CI: 4.13~8.31]；$P < 0.05$）均有改善。其他终点指标在两组间无显著差异。两组间不良事件相似。

Conclusions: Yuxintong capsule, as an adjunctive therapy to conventional treatment, improved AT, and general health and vitality scores on SF-36 scale in patients with stable CHD.

However, the improvements in VO2peak, METs, and the duration and onset time of 1-mm ST-segment depression on ECG were not statistically significant.

结论：愈心痛胶囊作为常规治疗的辅助疗法，可改善稳定型冠心病患者的无氧阈，以及 SF-36 量表中的总体健康和活力评分。然而，VO2peak、METs 及心电图上 1mm ST 段压低的持续时间和发生时间的改善未达到统计学显著性。

Keywords: Stable coronary heart disease; Yuxintong capsule; Cardiopulmonary fitness; Cardiopulmonary exercise test

关键词：稳定型冠心病；愈心痛胶囊；心肺耐力；心肺运动试验

Abbreviations: AT, anaerobic threshold; ACS, acute coronary syndrome; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; CRF, cardiopulmonary fitness; CPET, cardiopulmonary exercise test; CYTA, Corydalis yanhusuo total alkaloids; CONSORT, Consolidated Standards of Reporting Trials; CRO, contract research organization; DSMB, data and safety monitoring board; ECG, electrocardiography; FAS, full analysis set; LSMD, least squares mean difference; METs, metabolic equivalents; MedDRA, Medical Dictionary for Regulatory Activities; NYHA, New York Heart Association; PPS, per protocol set; ROS, reactive oxygen species; RER, respiratory exchange ratio; SAQ, Seattle Angina Questionnaire; SF-36, 36-Item Short Form Health Survey; SS, safety set; SUSARs, suspected unexpected serious adverse reactions; VO2peak, peak oxygen uptake.

缩略语：AT，无氧阈；ACS，急性冠脉综合征；BMI，体质指数；CHD，冠心病；CVD，心血管疾病；CRF，心肺耐力；CPET，心肺运动试验；CYTA，延胡索总生物碱；CONSORT，临床试验报告统一标准；CRO，合同研究组织；DSMB，数据安全监察委员会；ECG，心电图；FAS，全分析集；LSMD，最小二乘均值差；METs，代谢当量；MedDRA，监管活动医学词典；NYHA，纽约心脏协会；PPS，符合方案集；ROS，活性氧；RER，呼吸交换比；SAQ，西雅图心绞痛问卷；SF-36，36 项健康调查简表；SS，安全集；SUSARs，可疑非预期严重不良反应；VO2peak，峰值摄氧量。

1. Introduction

1. 引言

Despite recent advances in drugs and interventions for coronary heart disease (CHD), many patients continue to experience reduced quality of life and impaired cardiopulmonary fitness (CRF) (Al-Lamee et al., 2018; Rezende et al., 2013; Boden et al., 2007). CRF is a critical physiological indicator of the integrated capacity of the circulatory and respiratory systems to deliver oxygen during exercise (Fan et al., 2020) and is recognized as an independent predictor of cardiovascular disease (CVD) mortality (Ross et al., 2016). In patients with CHD, coronary artery stenosis induces ischemic and hypoxic injury to cardiomyocytes and triggers elevated intracellular reactive oxygen species (ROS), Ca^{2+} overload, and impaired mitochondrial energy synthesis, which contribute to a decline the patients' CRF (Levraut et al., 2003; Chang et al., 2023).

尽管冠心病药物和介入治疗取得了最新进展，但许多患者仍持续存在生活质量下降和心肺功能受损的问题（Al-Lamee et al., 2018；Rezende et al., 2013；Boden et al., 2007）。心肺功能是衡量循环和呼吸系统在运动时输送氧气综合能力的关键生理指标（Fan et al., 2020），并被公认为心血管疾病死亡率的独立预测因子（Ross et al., 2016）。在冠心病患者中，冠状动脉狭窄诱导心肌细胞缺血缺氧损伤，并引发细胞内活性氧升高、钙超载和线粒体能量合成受损，这些因素共同导致患者心肺功能下降（Levraut et al., 2003；Chang et al., 2023）。

Yuxintong capsule was approved by the China Food and Drug Administration in 2002 (GYZZ20020089) for the treatment of CHD. It is produced by Dalian Shengguang Pharmaceutical Group Co., Ltd. The studies indicated that red ginseng extract reduced mitochondrial swelling and membrane permeability, enhanced mitochondrial biogenesis, and improved mitochondrial dysfunction (Zhang et al., 2022; Yang et al., 2022). Ginsenosides Rg1 and Rb1 from red ginseng promoted aerobic respiration and SIRT1-driven mitochondrial biogenesis in cardiomyocytes (Huang et al., 2022). Notoginsenosides, the primary active components of Panax notoginseng, enhanced mitophagy, reduced mitochondrial ROS, increased mitochondrial membrane potential and oxygen consumption rate, and diminished oxidative stress injury (Zhou et al., 2018; Zhang et al., 2022). Corydalis yanhusuo total alkaloids (CYTA), the primary active components of Corydalis yanhusuo, possess both analgesic and cardioprotective properties. CYTA can reduce myocardial infarction area and improve cardiac function by suppressing oxidative stress, mitochondrial damage, apoptosis, and Ca^{2+} overload (Ling et al., 2006; Qi et al., 2024).

愈心痛胶囊于 2002 年获得中国食品药品监督管理局批准（国药准字 Z20020089）用于治疗冠心病。它由大连胜光药业集团有限公司生产。研究表明，红参提取物可减少线粒体肿胀和膜通透性，增强线粒体生物合成，并改善线粒体功能障碍（Zhang et al., 2022；Yang et al., 2022）。红参中的人参皂苷 Rg1 和 Rb1 可促进心肌细胞的有氧呼吸和 SIRT1 驱动的线粒体生物合成（Huang et al., 2022）。三七皂苷是三七的主要活性成分，可增强线粒体自噬，减少线粒体活性氧，增加线粒体膜电位和耗氧率，并减轻氧化应激损伤（Zhou et al., 2018；Zhang et al., 2022）。延胡索总生物碱是延胡索的主要活性成分，具有镇痛和心脏保护双重作用。延胡索总生物碱可通过抑制氧化应激、线粒体损伤、凋亡和钙超载来减少心肌梗死面积并改善心功能（Ling et al., 2006；Qi et al., 2024）。

Our previous studies with acute myocardial ischaemic dogs showed that Yuxintong capsule significantly reduced the area of myocardial infarction, increased the coronary blood flow (Lei et al., 1996), and inhibited the increase in creatine phosphokinase (Lei et al., 1997). The clinical studies demonstrated that Yuxintong capsule inhibited the inflammatory reaction, decreased the reliance on nitroglycerin consumption, alleviated angina symptoms, and promoted the recovery of ischaemic ST-segment changes on electrocardiography (ECG) in CHD patients (Wu et al., 2018; Wei, 2009). However, whether it improves CRF in patients with CHD remains unknown. Therefore, we conducted this clinical trial to evaluate the effects of Yuxintong capsule in combination with conventional Western medication treatment on CRF in patients with stable CHD.

我们前期在急性心肌缺血犬模型中的研究表明，愈心痛胶囊可显著缩小心肌梗死面积，增加冠脉血流量（Lei 等，1996），并抑制肌酸磷酸激酶的升高（Lei 等，1997）。临床研究表明，愈心痛胶囊可抑制炎症反应，减少硝酸甘油用量，缓解心绞痛症状，并促进冠心病患者心电图缺血性 ST 段改变的恢复（Wu 等，2018；Wei，2009）。然而，其能否改善冠心病患者的 CRF 尚不清楚。因此，我们开展了本项临床试验，以评估愈心痛胶囊联合常规西药治疗对稳定型冠心病患者 CRF 的影响。

2. Materials and methods

2. 材料与方法

2.1. Study design

2.1. 研究设计

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial registered with the Chinese Clinical Trial Registry (ChiCTR2000041293; December 23, 2020). Centralized randomization was performed, stratified by prescribed exercise intensity (low vs. moderate), using permuted blocks within strata (1:1 allocation). Following a 1-week screening period at 13 Grade A tertiary hospitals in mainland China, eligible patients were randomly assigned to the Yuxintong group or the placebo group at a 1:1 ratio for 12 weeks of treatment. Follow-up assessments were conducted at 8 and 12 weeks (±3 days) (Supplementary material 1).

本研究是一项多中心、随机、双盲、安慰剂对照、平行组临床试验，已在中国临床试验注册中心注册（ChiCTR2000041293；2020 年 12 月 23 日）。采用集中随机化，按规定的运动强度（低强度 vs. 中等强度）分层，并在各层内使用置换区组（1:1 分配）。在中国大陆 13 家三级甲等医院进行为期 1 周的筛选期后，符合条件的患者按 1:1 的比例随机分配至愈心痛组或安慰剂组，接受 12 周治疗。在第 8 周和第 12 周（±3 天）进行随访评估（补充材料 1）。

2.2. Ethics

2.2. 伦理

The study adhered to the guidelines of the Declaration of Helsinki of the World Medical Association (World Medical Association, 2013). Ethical approval was obtained from the ethics committees of each study center. All participants provided written informed consent and agreed to the publication of their data. We strictly adhered to the Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al., 2010) guidelines to report the results of this study (Supplementary material 2).

本研究遵循世界医学协会《赫尔辛基宣言》的指南（World Medical Association, 2013）。已获得各研究中心的伦理委员会批准。所有参与者均签署了书面知情同意书，并同意其数据发表。我们严格遵守《临床试验报告统一标准》指南（Schulz et al., 2010）报告本研究结果（补充材料 2）。

2.3. Study population

2.3. 研究人群

Patients were included in the present study if they met the following criteria: (1) aged between 18 and 75 years; (2) diagnosed with stable CHD according to the 2018 Chinese guidelines (Interventional Cardiology Group of Cardiovascular Branch of Chinese Medical Association, 2018), defined by coronary artery stenosis ≥50% on coronary angiography or coronary computed tomography angiography, or a clinically stable status for ≥3 months after percutaneous coronary intervention; (3) had symptoms of fatigue or shortness of breath, and typical effort angina; (4) had a history of previous myocardial infarction, or a documented diagnosis of heart failure (including heart failure with preserved ejection fraction); and (5) provided written informed consent.

符合以下标准的患者被纳入本研究：（1）年龄在 18 至 75 岁之间；（2）根据 2018 年中国指南（中华医学会心血管病学分会介入心脏病学组，2018）诊断为稳定型冠心病，定义为冠状动脉造影或冠状动脉 CT 血管成像显示冠状动脉狭窄≥50%，或经皮冠状动脉介入治疗后临床稳定状态≥3 个月；（3）有疲劳或气短症状，以及典型劳力性心绞痛；（4）有既往心肌梗死病史，或确诊为心力衰竭（包括射血分数保留的心力衰竭）；（5）签署书面知情同意书。

The exclusion criteria were as follows: (1) left main coronary artery stenosis (5th segment) ≥50% or proximal left anterior descending coronary artery stenosis (6th segment) >70%; (2) severe aortic stenosis, acute aortic dissection, acute myocarditis or pericarditis, aneurysm, severe pulmonary hypertension, acute pulmonary embolism, pulmonary infarction, emphysema, respiratory failure or other cardiorespiratory diseases; (3) uncontrolled blood pressure with systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg; (4) uncontrolled arrhythmia with clinical symptoms or haemodynamic disorders; (5) severe primary hepatic, renal, or haematopoietic system disorders, acute infectious diseases, mental disorders, or other diseases that would render the patient unsuitable for the CPET; (6) pregnancy, planning to achieve pregnancy or lactation; (7) major surgical intervention on the skull or chest and abdomen within 4 weeks and a bleeding tendency; (8) participated in other clinical trials within the past one month; and (9) allergy to the test drug or its known components.

排除标准如下：（1）左主干冠状动脉狭窄（第 5 段）≥50%或左前降支近端狭窄（第 6 段）>70%；（2）严重主动脉瓣狭窄、急性主动脉夹层、急性心肌炎或心包炎、动脉瘤、严重肺动脉高压、急性肺栓塞、肺梗死、肺气肿、呼吸衰竭或其他心肺疾病；（3）未控制的高血压，收缩压≥160 mmHg 和/或舒张压≥100 mmHg；（4）伴有临床症状或血流动力学紊乱的未控制心律失常；（5）严重的原发性肝脏、肾脏或造血系统疾病、急性

感染性疾病、精神障碍或其他使患者不适合进行心肺运动试验的疾病；（6）妊娠、计划妊娠或哺乳期；（7）4 周内进行过颅脑或胸腹部大手术，且有出血倾向；（8）过去一个月内参加过其他临床试验；（9）对试验药物或其已知成分过敏。

2.4. Sample size

2.4. 样本量

The primary outcomes were peak oxygen uptake (VO2peak) and the anaerobic threshold (AT). The trial hypothesis would be supported if a statistically significant between-group difference favoring the Yuxintong group over the placebo group was observed for either outcome. Superiority was tested using a two-sided α of 0.025 to control for multiplicity, with a superiority margin of 0 (Stefanos et al., 2020). The test power (1-β) was set at 80% with a 1:1 allocation ratio between groups. Based on clinical experience and previous literature (Li et al., 1999), we assumed that after 12 weeks of treatment, the changes in VO2peak would be 4.5 ± 4.9 $mL \cdot kg^{-1} \cdot min^{-1}$ in the Yuxintong group and 2.8 ± 4.9 $mL \cdot kg^{-1} \cdot min^{-1}$ in the placebo group. The corresponding changes in AT were assumed to be 0.25 ± 0.28 $mL \cdot kg^{-1} \cdot min^{-1}$ and 0.15 ± 0.28 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively. The sample size calculation indicated that 160 participants per group were needed for VO2peak and 151 for AT. To ensure adequate power for both outcomes and account for a 20% dropout rate, the final planned sample size was set at 404 participants.

主要终点为峰值摄氧量（VO2peak）和无氧阈（AT）。若任一终点指标观察到有利于愈心痛组优于安慰剂组的统计学显著组间差异，则试验假设成立。采用双侧α=0.025 进行优效性检验以控制多重性，优效性界值为 0（Stefanos 等，2020）。检验效能（1-β）设定为 80%，组间分配比例为 1:1。根据临床经验和既往文献（Li 等，1999），假设治疗 12 周后，愈心痛组 VO2peak 变化量为 4.5 ± 4.9 $mL \cdot kg^{-1} \cdot min^{-1}$，安慰剂组为 2.8 ± 4.9 $mL \cdot kg^{-1} \cdot min^{-1}$。相应的 AT 变化量分别假设为 0.25 ± 0.28 $mL \cdot kg^{-1} \cdot min^{-1}$和 0.15 ± 0.28 $mL \cdot kg^{-1} \cdot min^{-1}$。样本量计算表明，VO2peak 每组需 160 例，AT 每组需 151 例。为确保两个终点均有足够效能并考虑 20%的脱落率，最终计划样本量设定为 404 例。

2.5. Randomization and blinding

2.5. 随机化和盲法

Randomization was centralized with stratification by prescribed exercise intensity (low vs. moderate) and permuted blocks within strata (1:1 allocation). Allocation was concealed using a secure interactive web-response system. An independent statistician generated the randomization

schedule using SAS. Separate sequences for subjects and drug packs were created based on exercise intensity and the allocation ratio. Due to the unfixed sample size per stratum, block randomization was used independently for each, generating 404 codes per stratum (moderate: 001–404; low: 405–808) to accommodate the extreme scenario of all participants being enrolled in one stratum. Participants, investigators, care providers, endpoint adjudicators, and statisticians remained blinded. Placebo was indistinguishable from active product in appearance, taste, and packaging.

采用中心化随机方法，按处方运动强度（低强度 vs. 中等强度）分层，各层内使用置换区组法（1:1 分配）。采用安全的交互式网络应答系统隐藏分配。由独立统计师使用 SAS 生成随机化方案。根据运动强度和分配比例分别创建受试者和药物包装的独立序列。由于各层样本量不固定，各层独立使用区组随机化，每层生成 404 个编码（中等强度：001~404；低强度：405~808），以应对所有受试者均被纳入同一层的极端情况。受试者、研究者、护理提供者、终点判定者和统计师均保持盲态。安慰剂在外观、味道和包装上与试验药物无法区分。

2.6. Intervention

2.6. 干预措施

The specification of Yuxintong capsule/placebo is 0.33 g/capsule. Patients received treatment with 12 capsules (3.96 g) of Yuxintong capsule/placebo daily (4 capsules, 3 times daily for 12 weeks). High-performance liquid chromatography (HPLC) showed that the main active ingredients of Yuxintong capsule included tetrahydropalmatine, notoginsenoside R1, ginsenoside Rg1, ginsenoside Re, palmatine chloride, berberine hydrochloride, ginsenoside Rf, and ginsenoside Rb1, and we also used Liquid Chromatography Mass Spectrometer (LC/MS) to identify potential active ingredients in Yuxintong capsule (Supplementary material 3).

愈心痛胶囊/安慰剂规格为 0.33 g/粒。患者每日服用 12 粒（3.96 g）愈心痛胶囊/安慰剂（每次 4 粒，每日 3 次，连续 12 周）。高效液相色谱（HPLC）分析显示，愈心痛胶囊的主要活性成分包括延胡索乙素、三七皂苷 R1、人参皂苷 Rg1、人参皂苷 Re、盐酸巴马汀、盐酸小檗碱、人参皂苷 Rf 和人参皂苷 Rb1，我们还使用液相色谱-质谱联用仪（LC/MS）鉴定了愈心痛胶囊中的潜在活性成分（补充材料 3）。

In accordance with the 2018 "Guidelines on the Diagnosis and Treatment of Stable CHD" published by the Chinese Medical Association (Interventional Cardiology Group of

Cardiovascular Branch of Chinese Medical Association, 2018), all patients in this study were treated with symptom-relieving agents (nitrates), anti-ischaemic drugs (beta blockers and/or calcium channel blockers), antiplatelet drugs (aspirin or clopidogrel), and lipid-lowering drugs (statins). In addition, throughout the study, all participants received low-intensity or moderate-intensity exercise rehabilitation guidance based on their own circumstances (Fletcher et al., 2013). The patients were required to follow the guidance for home exercise three times a week. During the follow-up period, detailed information on the patient's rehabilitation exercise was recorded in a case report form.

根据中华医学会发布的 2018 年《稳定型冠心病诊断与治疗指南》（中华医学会心血管病学分会介入学组，2018），本研究中所有患者均接受缓解症状药物（硝酸酯类）、抗缺血药物（β受体阻滞剂和/或钙通道阻滞剂）、抗血小板药物（阿司匹林或氯吡格雷）和降脂药物（他汀类）治疗。此外，在整个研究期间，所有参与者均根据自身情况接受低强度或中等强度运动康复指导（Fletcher 等，2013）。患者被要求每周在家按指导运动 3 次。在随访期间，患者的详细运动康复信息记录在病例报告表中。

All participants underwent CPET on an electronically braked cycle ergometer (Jaeger MasterScreen CPX, Germany). A personalized ramp protocol was employed with the goal of eliciting exhaustion within 8–12 min. The protocol began with a 3-min warm-up at 20 W, followed by a continuous increase in work rate (10, 15, or 20 W per minute) until volitional exhaustion. The criteria for terminating the CPET included reaching the volitional exhaustion criterion (respiratory exchange ratio, RER ≥ 1.10) or the emergence of limiting symptoms, such as ischemic ECG changes, abnormal elevation or reduction in blood pressure, angina. The reasons for CPET termination and their respective proportions were detailed in supplementary material 4. During the test, a cardiologist continuously monitored the participants' ECG. The VO2peak was defined as the highest value averaged over eight breathing cycles. AT was determined using the V-slope method by two independent physicians who were blinded to allocation; discrepant readings were adjudicated by a third reviewer. Inter-reader agreement was assessed.

所有参与者在电动自行车功量计（Jaeger MasterScreen CPX，德国）上进行 CPET。采用个性化递增方案，目标是在 8~12 分钟内达到力竭。方案从 20 W 热身 3 分钟开始，随后以连续递增的功率（每分钟 10、15 或 20 W）直至主观力竭。终止 CPET 的标准包括达到力竭标准（呼吸交换比 RER ≥ 1.10）或出现限制性症状，如缺血性心电图改变、血压异常升高或降低、心绞痛。CPET 终止原因及其比例详见补充材料 4。测试期间，心血管科医

师持续监测参与者心电图。VO2peak 定义为 8 个呼吸周期平均值中的最高值。AT 由两名独立且不知晓分配的医师采用 V-slope 法判定；如有分歧，由第三位审阅者裁定。评估了读者间一致性。

2.7. Outcomes

2.7. 终点指标

The primary outcomes included VO2peak and AT. The secondary outcomes included metabolic equivalents (METs), the duration and onset time of 1-mm ST-segment depression on ECG, and 36-Item Short Form Health Survey (SF-36) scores. These outcomes were measured at baseline and at the 12-week endpoint. Additionally, at the 8-week time point, patient data on vital signs, rehabilitation exercise adherence, adverse events, and concomitant treatments were recorded. The safety of Yuxintong capsule was evaluated based on the incidence of all adverse events and adverse drug reactions observed throughout the trial.

主要终点包括 VO2peak 和 AT。次要终点包括代谢当量（METs）、心电图上 1mm ST 段压低的持续时间和发生时间，以及 36 项健康调查简表（SF-36）评分。上述指标在基线和第 12 周末进行测量。此外，在第 8 周时记录患者生命体征、运动康复依从性、不良事件和合并用药数据。愈心痛胶囊的安全性基于整个试验期间观察到的所有不良事件和药物不良反应发生率进行评估。

2.8. Data management and quality control

2.8. 数据管理和质量控制

An electronic data capture system was used for online data management in this study. Additionally, a Data and Safety Monitoring Board (DSMB) was convened to periodically review trial data, participant safety, study progress, and quality.

本研究使用电子数据采集系统进行在线数据管理。此外，成立了数据安全监察委员会（DSMB），定期审查试验数据、受试者安全、研究进展和质量。

2.9. Statistical analysis

2.9. 统计分析

In accordance with the intention-to-treat principle, the randomized subjects who received the trial drugs at least once and had at least one follow-up visit were included in the full analysis set

(FAS). Data for patients who were lost to follow-up were imputed using multiple imputation methods. The per protocol set (PPS) included patients who complete the trial without major deviations of protocol. The safety set (SS) included all patients who received at least one treatment after randomization and underwent the safety evaluation. To ensure the accuracy and representativeness of the research results, we analysed the FAS.

根据意向性治疗原则，至少接受过一次试验药物且至少有一次随访的随机受试者纳入全分析集（FAS）。失访患者数据采用多重插补法进行填补。符合方案集（PPS）包括完成试验且无重大方案偏离的患者。安全集（SS）包括随机化后至少接受一次治疗并进行安全性评估的所有患者。为确保研究结果的准确性和代表性，我们分析了 FAS。

The significance level for the primary outcomes was set at 0.025 (two-sided), whereas for the secondary outcomes, it was set at 0.05 (two-sided). For primary and key secondary endpoints, Analysis of Covariance (ANCOVA) was used (with the change from baseline as the outcome; and age, gender, BMI, baseline value, study center, exercise-intensity stratum, and beta-blocker use as covariates). Categorical data were presented in frequency tables and reported as percentages, and between-group differences were assessed with the chi-square test or Fisher's exact test. Continuous variables with a normal distribution are presented as mean ± standard deviation; otherwise, they are presented as median with interquartile range. Student's t-test or the Wilcoxon rank-sum test was used, as appropriate, to analyse between-group differences. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

主要终点的显著性水平设定为 0.025（双侧），次要终点设定为 0.05（双侧）。对于主要和关键次要终点，采用协方差分析（ANCOVA）（以基线变化值作为结局变量；以年龄、性别、BMI、基线值、研究中心、运动强度分层和β受体阻滞剂使用作为协变量）。分类数据以频数表呈现并报告百分比，组间差异采用卡方检验或 Fisher 精确检验评估。符合正态分布的连续变量以均值±标准差表示，否则以中位数和四分位距表示。根据情况采用 Student's t 检验或 Wilcoxon 秩和检验分析组间差异。所有分析均使用 SAS 9.4 软件（SAS Institute，Cary，NC，USA）进行。

3. Results

3. 结果

3.1. Baseline characteristics of patients

3.1. 患者基线特征

From March 2021 to November 2021, 422 patients were screened, of whom 18 did not meet the inclusion criteria. Finally, a total of 404 patients were enrolled and randomly divided into the Yuxintong group and the placebo group. A total of 60 patients (32 patients in the Yuxintong group and 28 patients in the placebo group) dropped out. According to the predefined statistical analysis plan, the full analysis set (FAS) comprised 369 patients, and the safety set (SS) comprised 393 patients (Fig. 1). There were no statistically significant differences in demographic information, comorbidities, beta-blocker use or exercise intensity between the two groups (Table 1).

2021 年 3 月至 2021 年 11 月，共筛查 422 例患者，其中 18 例不符合纳入标准。最终共入组 404 例患者，随机分为愈心痛组和安慰剂组。共 60 例患者脱落（愈心痛组 32 例，安慰剂组 28 例）。根据预定的统计分析计划，全分析集（FAS）包含 369 例，安全集（SS）包含 393 例（图 1）。两组间在人口学信息、合并症、β受体阻滞剂使用或运动强度方面无统计学显著差异（表 1）。

3.2. Exercise adherence

3.2. 运动依从性

Exercise adherence was summarized as sessions per week and the proportion achieving the prescribed intensity (heart-rate or RPE targets). The Yuxintong and placebo groups completed a median of 3 sessions per week, with target-intensity attainment of 91.4% and 93.2%, respectively.

运动依从性以每周运动次数和达到处方强度（心率或 RPE 目标值）的比例来汇总。愈心痛组和安慰剂组每周平均完成 3 次运动，目标强度达标率分别为 91.4%和 93.2%。

3.3. Primary outcomes

3.3. 主要终点

The within-group comparisons showed that after 12 weeks of treatment, Yuxintong group demonstrated significant improvements from baseline in both VO2peak (19.23 ± 4.97 vs. 19.98 ± 4.78 $mL \cdot kg^{-1} \cdot min^{-1}$, P = 0.002) and AT (12.44 ± 3.78 vs. 13.42 ± 3.54 $mL \cdot kg^{-1} \cdot min^{-1}$, P = 0.001). In contrast, no significant improvements were observed in placebo group for either VO2peak (19.67 ± 4.43 vs. 19.79 ± 4.87 $mL \cdot kg^{-1} \cdot min^{-1}$, P = 0.59) or AT (12.76 ± 3.29 vs. 12.87 ± 3.37 $mL \cdot kg^{-1} \cdot min^{-1}$, P = 0.57). For the between-group comparison, the improvement in AT was significantly greater in the Yuxintong group than in the placebo group (LSMD, 0.80 [95% CI:

0.28 to 1.32]; P < 0.025). However, the between-group difference for VO2peak did not reach statistical significance (LSMD, 0.57 [95% CI: 0.06 to 1.21]; P > 0.025). These results suggested that Yuxintong capsule may improve the AT in patients with stable CHD, but shows no significant improvement in VO2peak (Table 2 and Fig. 2).

组内比较显示，治疗 12 周后，愈心痛组 VO2peak（19.23 ± 4.97 vs. 19.98 ± 4.78 $mL \cdot kg^{-1} \cdot min^{-1}$，P = 0.002）和 AT（12.44 ± 3.78 vs. 13.42 ± 3.54 $mL \cdot kg^{-1} \cdot min^{-1}$，P = 0.001）均较基线显著改善。安慰剂组 VO2peak（19.67 ± 4.43 vs. 19.79 ± 4.87 $mL \cdot kg^{-1} \cdot min^{-1}$，P = 0.59）和 AT（12.76 ± 3.29 vs. 12.87 ± 3.37 $mL \cdot kg^{-1} \cdot min^{-1}$，P = 0.57）均未见显著改善。组间比较显示，愈心痛组 AT 的改善幅度显著大于安慰剂组（LSMD 0.80 [95% CI: 0.28~1.32]；P < 0.025）。然而，VO2peak 的组间差异未达到统计学显著性（LSMD 0.57 [95% CI: 0.06~1.21]；P > 0.025）。这些结果提示，愈心痛胶囊可改善稳定型冠心病患者的 AT，但对 VO2peak 无显著改善（表 2 和图 2）。

3.4. Secondary outcomes

3.4. 次要终点

Within-group comparisons revealed that after 12 weeks of treatment, Yuxintong group showed a significant increase in METs (5.31 ± 1.62 vs. 5.57 ± 1.46 MET, P = 0.001), and the placebo group also exhibited a significant improvement (5.33 ± 1.53 vs. 5.51 ± 1.48 MET, P = 0.026). However, between-group comparison demonstrated that the difference in METs was not statistically significant (0.25 ± 1.03 vs. 0.18 ± 1.08 MET; LSMD, 0.09 [95% CI: 0.10 to 0.29]; P > 0.05). These results suggest that Yuxintong capsule did not produce a statistically significant improvement in METs compared with placebo (Table 2 and Fig. 3).

组内比较显示，治疗 12 周后，愈心痛组 METs 显著增加（5.31 ± 1.62 vs. 5.57 ± 1.46 MET，P = 0.001），安慰剂组也有显著改善（5.33 ± 1.53 vs. 5.51 ± 1.48 MET，P = 0.026）。然而，组间比较显示 METs 的差异不具有统计学显著性（0.25 ± 1.03 vs. 0.18 ± 1.08 MET；LSMD 0.09 [95% CI: 0.10~0.29]；P > 0.05）。这些结果提示，与安慰剂相比，愈心痛胶囊对 METs 的改善未达到统计学显著性（表 2 和图 3）。

Among the subgroup of patients who exhibited exercise-induced ST-segment depression, changes in the onset time and the duration of 1-mm ST-segment depression were analyzed between the two groups. In within-group comparisons, after 12 weeks of treatment, the changes in the onset time of 1-mm ST-segment depression did not reach statistical significance in either

group (Yuxintong group: 6.23 ± 3.89 vs. 6.21 ± 4.15 min, P = 0.94; placebo group: 6.89 ± 2.89 vs. 6.75 ± 3.48 min, P = 0.55). Furthermore, the between-group difference in onset time was also not statistically significant (P = 0.78). Regarding the duration of 1-mm ST-segment depression, the Yuxintong group showed a slight shortening compared to baseline (4.68 ± 7.38 vs. 4.49 ± 7.44 min, P = 0.55), whereas the placebo group exhibited a slight prolongation (3.82 ± 3.44 vs. 3.97 ± 3.45 min, P = 0.66). But the between-group difference in duration was not significant (P = 0.48) (Table 3).

在出现运动诱发性 ST 段压低的患者亚组中，分析了两组患者 1mm ST 段压低发生时间和持续时间的变化。组内比较显示，治疗 12 周后，两组 1mm ST 段压低发生时间的变化均未达到统计学显著性（愈心痛组：6.23 ± 3.89 vs. 6.21 ± 4.15 min，P = 0.94；安慰剂组：6.89 ± 2.89 vs. 6.75 ± 3.48 min，P = 0.55）。此外，发生时间的组间差异也不具有统计学显著性（P = 0.78）。关于 1mm ST 段压低持续时间，愈心痛组较基线略有缩短（4.68 ± 7.38 vs. 4.49 ± 7.44 min，P = 0.55），而安慰剂组略有延长（3.82 ± 3.44 vs. 3.97 ± 3.45 min，P = 0.66）。但持续时间的组间差异不显著（P = 0.48）（表 3）。

Compared with the baseline, the scores of general health, physiological function, role-physical, role-emotional, social function, bodily pain, vitality and mental health on the SF-36 were significantly improved in both Yuxintong and placebo groups after 12 weeks of treatment (P < 0.05). Compared with those of placebo group, there was a significant difference in the scores of general health (13.61 ± 15.13 vs. 8.29 ± 14.14; LSMD 5.30, [95% CI: 2.33 to 8.31]; P < 0.05) and vitality (12.46 ± 11.32 vs. 6.01 ± 11.41; LSMD 6.43, [95% CI: 4.13 to 8.31]; P < 0.05) in Yuxintong group (Fig. 4).

与基线相比，治疗 12 周后，愈心痛组和安慰剂组 SF-36 中的总体健康、生理功能、生理职能、情感职能、社会功能、躯体疼痛、活力和精神健康评分均显著改善（P < 0.05）。与安慰剂组相比，愈心痛组在总体健康（13.61 ± 15.13 vs. 8.29 ± 14.14；LSMD 5.30 [95% CI: 2.33~8.31]；P < 0.05）和活力评分（12.46 ± 11.32 vs. 6.01 ± 11.41；LSMD 6.43 [95% CI: 4.13~8.31]；P < 0.05）方面存在显著差异（图 4）。

3.5. Adverse events

3.5. 不良事件

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class/preferred term (Supplementary material 5),

severity (graded by CTCAE criteria), and relationship to study drug. We report AE risk differences with 95% CIs, AEs leading to discontinuation, and serious AEs with narratives and causality assessment. And there were no significant differences in the number of AEs between two groups (32 [16.16%] vs. 24 [12.31%]; P = 0.27; Table 4). Among them, the most common AEs were gastrointestinal disorders, including 10 cases in the Yuxintong group (3 cases of abdominal pain; 2 cases of dyspepsia; 2 cases of diarrhea; 2 cases of nausea/vomiting; 1 case of gastritis) and 4 cases in the control group (2 cases of gastric distension; 1 case of dyspepsia; 1 case of gastritis).

不良事件（AEs）使用《监管活动医学词典》（MedDRA）进行编码，并按系统器官分类/首选术语（补充材料 5）、严重程度（根据 CTCAE 标准分级）以及与试验药物的关系进行总结。我们报告了不良事件风险差异及其 95%置信区间、导致停药的不良事件以及严重不良事件，并附有叙述和因果关系评估。两组之间的不良事件数量无显著差异（32 例[16.16%] vs. 24 例[12.31%]；P=0.27；表 4）。其中，最常见的不良事件是胃肠道疾病，包括愈心痛组 10 例（腹痛 3 例；消化不良 2 例；腹泻 2 例；恶心/呕吐 2 例；胃炎 1 例）和对照组 4 例（胃胀 2 例；消化不良 1 例；胃炎 1 例）。

Two Serious Adverse Events (SAEs) occurred in the placebo group (1 case of cholecystitis and 1 case of sudden death), while no SAEs were reported in the Yuxintong group. In the placebo group, a 68-year-old male patient (enrolled on April 30, 2021) with a history of myocardial infarction, percutaneous coronary intervention, hypertension, hyperlipidemia, and diabetes experienced sudden cardiac death on June 20, 2021. This event was assessed by the attending physician as unrelated to the study drug. No bleeding events or serious adverse reactions occurred. Participant safety was the primary concern in managing AEs. Based on the event's nature and severity, our responses included trial discontinuation, dose adjustment, symptomatic treatment, or observation. All Suspected Unexpected Serious Adverse Reactions (SUSARs) were reported to relevant authorities by investigators within required timelines, and promptly disseminated to all trial sites and ethics committees by the Contract Research Organization (CRO). And all SAEs were followed until a definitive outcome was reached, such as resolution, stabilization, death, or attribution to non-trial-related causes.

安慰剂组发生了 2 例严重不良事件（胆囊炎 1 例，猝死 1 例），而愈心痛组未报告严重不良事件。在安慰剂组中，一名 68 岁男性患者（于 2021 年 4 月 30 日入组），有心肌梗死、经皮冠状动脉介入治疗、高血压、高脂血症和糖尿病病史，于 2021 年 6 月 20 日发生心源性猝死。该事件经主治医师评估为与试验药物无关。未发生出血事件或严重不良反

应。参与者安全是管理不良事件的首要关注点。根据事件的性质和严重程度，我们的应对措施包括停止试验、调整剂量、对症治疗或观察。所有可疑的意外严重不良反应（SUSARs）均由研究者按规定时限报告给相关主管部门，并由合同研究组织（CRO）及时传达至所有试验中心和伦理委员会。所有严重不良事件均被随访至得出明确结局，例如缓解、稳定、死亡或归因于非试验相关原因。

4. Discussion

4. 讨论

To our knowledge, this is the first multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy of the Yuxintong capsule on CRF in patients with stable CHD. Individualized exercise intensity was prescribed based on the each patient's condition, and randomization was stratified by exercise intensity. This approach ensured the balance of exercise intensity between the Yuxintong group and the placebo group, while also enhancing patient compliance. Compared with baseline, the Yuxintong group showed significant improvements in the primary outcomes, including VO2peak and AT, as well as in secondary outcomes such as METs and SF-36 scores. Furthermore, compared with the placebo group, the Yuxintong group demonstrated superior improvement in the primary outcome of AT and in the general health and vitality domains of the SF-36.

据我们所知，这是首个评估愈心痛胶囊对稳定型冠心病患者 CRF 疗效的多中心、随机、双盲、安慰剂对照、平行组试验。根据每位患者的病情处方个体化运动强度，并按运动强度进行随机化分层。该方法确保了愈心痛组和安慰剂组之间运动强度的平衡，同时提高了患者的依从性。与基线相比，愈心痛组在主要终点（包括 VO2peak 和 AT）以及次要终点（如 METs 和 SF-36 评分）方面均有显著改善。此外，与安慰剂组相比，愈心痛组在主要终点 AT 以及 SF-36 的总体健康和活力维度方面表现出更优的改善。

In 2016, the American Heart Association recommended "CRF" as an important clinical "vital sign", urging healthcare providers to prioritize the assessment of this condition (Ross et al., 2016). CPET can objectively quantify the patient's CRF, and is commonly used to guide personalized exercise prescription for patients with CHD. It has high predictive value of recurrent cardiovascular events and is currently recognized as the best method to quantify CRF (Sun et al., 2010; Guazzi et al., 2012, 2017). VO2peak and AT are the most crucial indicators for clinical

evaluation of CRF. VO2peak refers to the oxygen uptake at where the participants are unable to maintain a continuous increase in power during exercise, which is an accurate indicator for evaluating exercise ability (Lewis et al., 2017). Terence et al. followed 12,169 male patients with CHD for an average of 7.9 years and reported that VO2peak was an independent predictor of the cardiac and all-cause mortality risks (Kavanagh et al., 2002). The AT, also well known as the lactic acid threshold or ventilation threshold, represents the point at where the body transitions from aerobic to anaerobic metabolism. The AT value can help patients safely engage in aerobic exercise within an appropriate range of CRF (Gibbons, 1987).

2016 年，美国心脏协会将“CRF”推荐为重要的临床“生命体征”，敦促医疗服务提供者优先评估这一指标（Ross 等，2016）。CPET 可客观定量评估患者的 CRF，常用于指导冠心病患者的个体化运动处方。其对复发性心血管事件具有较高的预测价值，是目前公认的定量评估 CRF 的最佳方法（Sun 等，2010；Guazzi 等，2012，2017）。VO2peak 和 AT 是临床评估 CRF 最重要的指标。VO2peak 是指参与者在运动中无法持续增加功率时的摄氧量，是评估运动能力的准确指标（Lewis 等，2017）。Terence 等对 12,169 例男性冠心病患者平均随访 7.9 年，报告 VO2peak 是心脏死亡和全因死亡风险的独立预测因子（Kavanagh 等，2002）。AT，也称为乳酸阈或通气阈，代表机体从有氧代谢向无氧代谢转换的临界点。AT 值可帮助患者在适当的 CRF 范围内安全进行有氧运动（Gibbons，1987）。

According to U.S. epidemiological data, the AT for middle-aged nonmanual workers aged 34–74 years should exceed 40% of maximal oxygen uptake. Patients with CHD often experience angina pectoris during excessive exercise, leading to limited daily activities and reduced skeletal muscle activity. And the CPET was often terminated prematurely due to symptom limitation. The AT excludes subjective factors and is therefore more sensitive than VO2peak in quantifying CRF (Fletcher et al., 2013). The results of the present study indicated that compared with placebo, Yuxintong capsule in addition to conventional Western medications for 12 weeks significantly increased AT, suggesting that the effective oxygen uptake was improved during the transition from aerobic to anaerobic metabolism.

根据美国流行病学数据，34~74 岁中年脑力劳动者的 AT 应超过最大摄氧量的 40%。冠心病患者在过度运动时常出现心绞痛，导致日常活动受限和骨骼肌活动减少。CPET 常因症状限制而过早终止。AT 排除了主观因素，因此在定量评估 CRF 方面比 VO2peak 更敏感（Fletcher 等，2013）。本研究结果表明，与安慰剂相比，愈心痛胶囊联合常规西药治疗 12 周可显著提高 AT，提示在有氧代谢向无氧代谢转换过程中有效摄氧量得到改善。

The body's aerobic capacity is closely related to mitochondrial function (Chance et al., 1955). A study showed that the ginsenosides in red ginseng reduced myocardial oxygen consumption, increased ischaemic myocardial tolerance, eliminated free radicals, inhibited lipid peroxidation, and minimized oxidative stress-induced mitochondrial damage (Piao et al., 2019). Ginsenosides regulated mitochondrial oxidative phosphorylation, energy metabolism, biosynthesis, apoptosis, mitophagy, and the status of membrane channels, thereby improving the mitochondrial oxidative energy supply capacity (Jiang et al., 2021; Wang et al., 2020). These findings provide a potential mechanistic rationale for the observed improvement in AT following Yuxintong capsule treatment in patients with stable CHD.

机体的有氧能力与线粒体功能密切相关（Chance 等，1955）。研究表明，红参中的人参皂苷可降低心肌耗氧量，提高缺血心肌耐受力，清除自由基，抑制脂质过氧化，并减轻氧化应激诱导的线粒体损伤（Piao 等，2019）。人参皂苷可调节线粒体氧化磷酸化、能量代谢、生物合成、细胞凋亡、线粒体自噬和膜通道状态，从而改善线粒体氧化供能能力（Jiang 等，2021；Wang 等，2020）。这些发现为愈心痛胶囊改善稳定型冠心病患者 AT 提供了潜在的作用机制依据。

In our study, the total scores of the SF-36 improved significantly after treatment in both the Yuxintong and placebo groups. Furthermore, compared with the placebo group, the Yuxintong group showed greater improvements in the general health and vitality scores of the SF-36. Previous studies have shown that the saponins of Panax notoginseng, a component of Yuxintong capsule, improved glucose uptake and absorption by skeletal muscle, increased the blood oxygen content in the myocardium, and decreased myocardial oxygen consumption (Yuan et al., 2012; Kitamura et al., 2017). Corydalis yanhusuo protected the myocardium by resisting myocardial ischemia and reducing apoptosis of cardiomyocytes (Li et al., 2017). Red ginseng can increase the antioxidant capacity of skeletal muscle and the myocardium in rats, while its extracts can improve the contractility and strength of skeletal muscle during exercise (Shin et al., 2020). These findings indicated the potential mechanisms by which Yuxintong capsule improved the general health and vitality scores on the SF-36 for patients with stable CHD.

在本研究中，愈心痛组和安慰剂组治疗后 SF-36 总分均显著改善。此外，与安慰剂组相比，愈心痛组在 SF-36 的总体健康和活力评分方面表现出更大幅度的改善。既往研究表明，愈心痛胶囊成分之一的三七皂苷可改善骨骼肌的葡萄糖摄取和吸收，增加心肌血氧含量，降低心肌耗氧量（Yuan 等，2012；Kitamura 等，2017）。延胡索通过抗心肌缺血和减少心肌细胞凋亡来保护心肌（Li 等，2017）。红参可提高大鼠骨骼肌和心肌的抗氧化能

力，其提取物可改善运动过程中骨骼肌的收缩力和力量（Shin 等，2020）。这些发现提示了愈心痛胶囊改善稳定型冠心病患者 SF-36 总体健康和活力评分的潜在机制。

Several limitations of this study should be noted. First, this study was conducted during the COVID-19 pandemic, and patients quarantine measures hindered normal follow-up, which was a primary reason for the 15% dropout rate. Second, the follow-up period was only three months, which may explain why the improvements in efficacy indicators did not reach statistical significance. Finally, our trial included only patients from mainland China, and further studies are needed to determine whether the findings are applicable to patients of different races.

本研究存在若干局限性。首先，本研究在 COVID-19 疫情期间开展，患者隔离措施阻碍了正常随访，这是 15%脱落率的主要原因。其次，随访期仅为三个月，这可能解释了疗效指标的改善未达到统计学显著性的原因。最后，本试验仅纳入来自中国大陆的患者，尚需进一步研究以确定研究结果是否适用于不同种族的患者。

5. Conclusion

5. 结论

Yuxintong capsule, as an adjunctive therapy to conventional treatment, improved AT, and general health and vitality scores on the SF-36 scale in patients with stable CHD.

愈心痛胶囊作为常规治疗的辅助疗法，可改善稳定型冠心病患者的无氧阈，以及 SF-36 量表中的总体健康和活力评分。

CRediT authorship contribution statement

CRediT 作者贡献声明

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Investigation. Zhaoqi Huang: Investigation. Ling Feng: Investigation. Yixin Wang: Investigation. Yan Feng: Investigation. Jie Zhang: Investigation. Mei Xue: Writing – review & editing, Funding acquisition, Formal analysis. Hao Xu: Project administration, Investigation. Dazhuo Shi: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. Keji Chen: Writing – review & editing, Investigation.

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Author agreement

作者声明

All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

所有数据均为内部生成，未使用论文代写。所有作者同意对确保工作完整性和准确性的各个方面负责。

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Declaration of competing interest

利益冲突声明

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

作者声明不存在可能影响本文报告工作的已知竞争性经济利益或个人关系。

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Appendix A. Supplementary data

附录 A. 补充数据

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2026.121169.

本文的补充数据可在以下网址在线获取：https://doi.org/10.1016/j.jep.2026.121169。

Data availability

数据可获得性

Data will be made available on request.

数据可根据要求提供。

Tables

表格

Table 1. Baseline characteristics of the study population

表 1. 研究人群的基线特征

The data were presented as the means ± standard deviations (SDs) or frequencies (percentages). There were no statistically significant differences in demographic information, comorbidities, beta-blocker use or exercise intensity between the two groups.

数据以均值±标准差（SD）或频数（百分比）表示。两组间在人口学信息、合并症、β受体阻滞剂使用或运动强度方面无统计学显著差异。

Table 2. Primary and key secondary outcomes (ITT analysis)

表 2. 主要和关键次要终点（ITT 分析）

VO2peak: Yuxintong group baseline 19.23 ± 4.97, 12 weeks 19.98 ± 4.78, difference 0.77 ± 3.35; Placebo group baseline 19.67 ± 4.43, 12 weeks 19.79 ± 4.87, difference 0.13 ± 3.19; LSMD 0.57 (-0.06, 1.21), unadjusted P = 0.066, adjusted P = 0.078. AT: Yuxintong group baseline 12.44 ± 3.78, 12 weeks 13.42 ± 3.54, difference 0.98 ± 2.88; Placebo group baseline 12.76 ± 3.29, 12 weeks 12.87 ± 3.37, difference 0.12 ± 2.79; LSMD 0.80 (0.28, 1.32), unadjusted P = 0.004, adjusted P = 0.003. METs: Yuxintong group baseline 5.31 ± 1.62, 12 weeks 5.57 ± 1.46, difference 0.25 ± 1.03; Placebo group baseline 5.33 ± 1.53, 12 weeks 5.51 ± 1.48, difference 0.18 ± 1.08; LSMD 0.09 (-0.10, 0.29), unadjusted P = 0.49, adjusted P = 0.34. Adjusted P-value: adjusted for age, sex, BMI, baseline, center, exercise intensity, and beta-blocker use.

VO2peak：愈心痛组基线 19.23 ± 4.97，12 周 19.98 ± 4.78，差值 0.77 ± 3.35；安慰剂组基线 19.67 ± 4.43，12 周 19.79 ± 4.87，差值 0.13 ± 3.19；LSMD 0.57（-0.06, 1.21），未校正 P = 0.066，校正后 P = 0.078。AT：愈心痛组基线 12.44 ± 3.78，12 周 13.42 ± 3.54，

差值 0.98 ± 2.88；安慰剂组基线 12.76 ± 3.29，12 周 12.87 ± 3.37，差值 0.12 ± 2.79；LSMD 0.80（0.28, 1.32），未校正 P = 0.004，校正后 P = 0.003。METs：愈心痛组基线 5.31 ± 1.62，12 周 5.57 ± 1.46，差值 0.25 ± 1.03；安慰剂组基线 5.33 ± 1.53，12 周 5.51 ± 1.48，差值 0.18 ± 1.08；LSMD 0.09（-0.10, 0.29），未校正 P = 0.49，校正后 P = 0.34。校正 P 值：校正年龄、性别、BMI、基线、中心、运动强度和β受体阻滞剂使用。

Table 3. The start and duration of 1 mm ST-segment depression during CPET

表 3. CPET 期间 1mm ST 段压低的起始时间和持续时间

ST-1mm start time (min): Yuxintong group (n=25) baseline 6.23 ± 3.89, 12 weeks 6.21 ± 4.15, difference -0.03 ± 1.68; Placebo group (n=32) baseline 6.89 ± 2.89, 12 weeks 6.75 ± 3.48, difference -0.14 ± 1.31. ST-1mm duration (min): Yuxintong group baseline 4.68 ± 7.38, 12 weeks 4.49 ± 7.44, difference -0.19 ± 1.54; Placebo group baseline 3.82 ± 3.44, 12 weeks 3.97 ± 3.45, difference 0.16 ± 2.00. The data were presented as the means ± SDs.

ST-1mm 发生时间（min）：愈心痛组（n=25）基线 6.23 ± 3.89，12 周 6.21 ± 4.15，差值-0.03 ± 1.68；安慰剂组（n=32）基线 6.89 ± 2.89，12 周 6.75 ± 3.48，差值-0.14 ± 1.31。ST-1mm 持续时间（min）：愈心痛组基线 4.68 ± 7.38，12 周 4.49 ± 7.44，差值-0.19 ± 1.54；安慰剂组基线 3.82 ± 3.44，12 周 3.97 ± 3.45，差值 0.16 ± 2.00。数据以均值±标准差表示。

Table 4. Adverse events in the SS

表 4. 安全集中的不良事件

Adverse events: Yuxintong group (n=198) 32 cases (16.16%, 95% CI: 11.05–21.27); Placebo group (n=195) 24 cases (12.31%, 95% CI: 7.44–16.56); P = 0.27. Mild adverse events: 31 (15.66%) vs. 19 (10.77%). Moderate adverse events: 1 (0.51%) vs. 3 (1.54%). Serious adverse events: 0 vs. 2 (1.03%). Adverse reactions: 4 (2.02%) vs. 2 (1.0%); P = 0.68. AE-related discontinuation: 2 (1.01%) vs. 2 (1.0%); P = 1. Relationship between study drug and AE: definitely related 0 vs. 0; probably related 0 vs. 0; possibly related 0 vs. 0; unlikely related 8 (4.04%) vs. 6 (3.08%); unrelated 24 (12.12%) vs. 18 (7.69%).

不良事件：愈心痛组（n=198）32 例（16.16%，95% CI: 11.05~21.27）；安慰剂组（n=195）24 例（12.31%，95% CI: 7.44~16.56）；P = 0.27。轻度不良事件：31（15.66%）vs. 19（10.77%）。中度不良事件：1（0.51%）vs. 3（1.54%）。严重不良事

件：0 vs. 2（1.03%）。药物不良反应：4（2.02%）vs. 2（1.0%）；P = 0.68。AE 相关停药：2（1.01%）vs. 2（1.0%）；P = 1。试验药物与 AE 的关系：肯定相关 0 vs. 0；很可能相关 0 vs. 0；可能相关 0 vs. 0；可能无关 8（4.04%）vs. 6（3.08%）；无关 24（12.12%）vs. 18（7.69%）。

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