

Original Article

Randomized Trial of a Tailored Exercise Protocol Versus Standard Cardiac Rehab for Reversing Microvascular Dysfunction Post-Stent

Muhsin Zia Muhammad¹, Serish Fatima², Humzah Syed Kahlid³, Muhammad Akram^{4*}, Ehab Noori Ahmed Tlala⁵, Neehal Shahid⁶

¹ MBBS, Ayub Medical College, Abbottabad, Pakistan

² Casualty Medical Officer, Benazir Bhutto Hospital, Rawalpindi, Pakistan

³ Quaid-e-Azam Medical College, Bahawalpur, Pakistan

⁴ ER Medical Officer, Shaheed Nawab Ghous Buksh Memorial Hospital, Mastung, Balochistan, Pakistan

⁵ European University, Tbilisi, Georgia

⁶ MS CPPT, The University of Lahore (UOL), Lahore, Pakistan.

✉ Correspondence: Muhammad Akram, aryanarish67@gmail.com

Received: 17 February 2026

Revised: 27 February 2026

Accepted: 10 March 2026

Published: 15 March 2026

HOW TO CITE

Muhsin Zia Muhammad et al. 2026. Randomized Trial of a Tailored Exercise Protocol Versus Standard Cardiac Rehab for Reversing Microvascular Dysfunction Post-Stent. Journal of Health, Wellness and Community Research. 4, 5 (Mar. 2026), 1–9.
DOI:https://doi.org/10.61919/dcnw5055

ARTICLE INFORMATION

Author Contributions	Concept: MZM, MA; Design: MZM, SF, MA; Data Collection: HSK, ENAT, NS; Analysis: MZM, MA, NS; Drafting: MZM, SF, HSK, MA, ENAT, NS.
Ethical Approval	The study was approved by research ethical board of Ayub Medical College, Abbottabad, Pakistan
Informed Consent	Written informed consent was obtained from all participants
Conflict of Interest	The authors declare no conflict of interest.
Funding	No external funding.
Data Availability	Available from the corresponding author on reasonable request.
AI Declaration	No generative AI was used for conceptualization, analysis, or content generation. AI use was limited to language refinement, and the authors remain fully responsible for the accuracy, originality, validity, and integrity of the manuscript's content.

ABSTRACT

Background: Coronary microvascular dysfunction may persist after successful percutaneous coronary intervention (PCI) and contribute to incomplete physiological and functional recovery. Individualized exercise rehabilitation may provide greater benefit than conventional rehabilitation. **Objective:** To compare the effects of a tailored exercise protocol with standard cardiac rehabilitation on coronary microvascular function after PCI. **Methods:** This two-arm randomized controlled trial included 100 post-PCI patients with documented coronary microvascular dysfunction at a tertiary care hospital in Lahore, Pakistan. Participants were randomized to tailored exercise (n=50) or standard cardiac rehabilitation (n=50) and followed for 12 months. The primary outcome was change in coronary flow reserve (CFR); secondary outcomes included index of microcirculatory resistance (IMR), VO₂peak, flow-mediated dilation (FMD), biochemical markers, and health-related quality of life. Longitudinal outcomes were analyzed using repeated-measures methods with intention-to-treat analysis. **Results:** CFR increased by 0.76 ± 0.24 in the tailored group versus 0.36 ± 0.22 in controls, yielding a between-group difference of 0.40 (95% CI 0.31–0.49; p<0.001). IMR decreased by 8.5 ± 3.7 versus 4.6 ± 3.1, respectively, with a between-group difference of –3.90 (95% CI –5.26 to –2.54; p<0.001). Greater improvements were also observed in VO₂peak, FMD, nitric oxide, hs-CRP, and physical and emotional quality-of-life domains. No major adverse events were reported. **Conclusion:** Tailored rehabilitation was associated with greater improvement in coronary microvascular, functional, endothelial, and selected patient-reported outcomes than standard rehabilitation over 12 months. **Keywords:** Cardiac Rehabilitation; Coronary Microvascular Dysfunction; Exercise Therapy; Percutaneous Coronary Intervention; Coronary Flow Reserve; Quality of Life.

INTRODUCTION

Coronary artery disease remains a major cause of cardiovascular morbidity and mortality, and percutaneous coronary intervention (PCI) is widely used to restore epicardial coronary blood flow in patients with clinically significant coronary obstruction. Advances in contemporary PCI have improved procedural success and revascularization outcomes; however, restoration of epicardial vessel patency does not invariably result in

complete resolution of ischemic symptoms or normalization of myocardial perfusion. A proportion of patients continue to experience angina, dyspnea, or reduced exercise capacity after technically successful PCI, indicating that mechanisms beyond residual epicardial stenosis may contribute to persistent symptoms (1,2).

Coronary microvascular dysfunction (CMD) is increasingly recognized as one potential contributor to impaired myocardial perfusion after PCI. Unlike obstructive disease of the major epicardial arteries, CMD reflects abnormal regulation of the small coronary vessels and may manifest as impaired vasodilatory reserve or increased microvascular resistance. Physiological assessment of the coronary microcirculation using indices such as coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR) allows quantification of these abnormalities and may provide prognostic information following PCI (3). Persistent abnormalities in coronary physiology are clinically important because successful epicardial intervention alone may not fully address the mechanisms responsible for post-procedural symptoms and impaired functional recovery (1,3).

Exercise-based cardiac rehabilitation is an established component of recovery after coronary revascularization because it improves functional capacity, cardiovascular conditioning, and overall recovery following coronary intervention. Nevertheless, conventional rehabilitation programs commonly prescribe broadly standardized exercise intensities and modalities, whereas exercise tolerance, ventricular function, comorbidity burden, vascular function, and physiological response vary substantially between patients. This variability provides a rationale for individualized exercise prescription, particularly in patients with documented CMD, in whom the therapeutic objective extends beyond general conditioning to improvement in vascular and microcirculatory function.

A personalized rehabilitation strategy may therefore be particularly relevant after PCI. Cardiopulmonary exercise testing can provide objective information on exercise capacity and support individualized intensity prescription, while coronary physiological indices can characterize the severity of microvascular impairment. Integrating these measures into exercise planning offers a potential method of adapting training intensity and progression to the physiological status of the individual patient. Such an approach is biologically plausible because repeated exercise increases vascular shear stress, improves cardiovascular conditioning, and may favor endothelial adaptation. However, improvements in peripheral vascular or exercise-related measures should not automatically be assumed to represent recovery of the coronary microcirculation; direct assessment of coronary physiological outcomes is therefore required.

Although contemporary PCI research increasingly emphasizes physiological characterization and individualized treatment strategies, much of the available literature has focused on procedural optimization, epicardial coronary physiology, stent-related outcomes, or prediction of adverse events rather than rehabilitation specifically directed at post-PCI microvascular recovery (3–5). Similarly, persistent symptoms after PCI may have multiple mechanisms, emphasizing the importance of identifying and targeting abnormalities not corrected by epicardial revascularization alone (1). Evidence directly comparing a physiology-informed, individualized exercise program with standard cardiac rehabilitation using CFR and IMR as coronary microvascular outcomes remains limited.

Accordingly, the present randomized controlled trial was designed to determine whether a tailored exercise protocol provides greater improvement in coronary microvascular function than standard cardiac rehabilitation in patients with documented CMD following PCI. The primary objective was to compare the change in CFR between groups over 12 months, while secondary outcomes included IMR, peak oxygen uptake ($\text{VO}_{2\text{peak}}$), flow-mediated dilation, circulating endothelial and inflammatory biomarkers, and health-related quality of life. It was hypothesized that the tailored exercise program would produce a greater improvement in coronary microvascular function and functional capacity than standard rehabilitation.

MATERIAL AND METHODS

This two-arm, parallel-group randomized controlled trial was conducted at a tertiary care hospital in Lahore, Pakistan, to compare the effects of a tailored exercise protocol with standard cardiac rehabilitation on coronary microvascular function following successful percutaneous coronary intervention (PCI). Participants were allocated in a 1:1 ratio and followed for 12 months. The trial was designed to evaluate whether exercise prescribed according to individual functional and coronary physiological characteristics produced greater improvement in microvascular function than conventional rehabilitation. All study procedures were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Ethical approval was obtained from the institutional review

board of the participating institution, and written informed consent was obtained from all participants before enrollment and initiation of study procedures.

Adults aged 40–75 years who had undergone PCI with stent implantation for stable or unstable angina within the preceding two weeks were assessed for eligibility. Participants were required to be clinically stable, have a left ventricular ejection fraction of at least 45%, be medically cleared by their treating cardiologist to undertake supervised exercise, and demonstrate evidence of post-PCI coronary microvascular dysfunction. Coronary microvascular dysfunction was defined as a coronary flow reserve (CFR) of ≤ 2.5 or an index of microcirculatory resistance (IMR) of ≥ 25 , determined using invasive coronary physiological assessment with a pressure–temperature sensor-tipped guidewire. Patients with New York Heart Association class III or IV heart failure, uncontrolled cardiac arrhythmias, uncontrolled hypertension exceeding 180/110 mmHg, myocardial infarction within the preceding seven days, or orthopedic or neurological conditions that substantially limited exercise participation were excluded. Patients with other comorbid conditions considered likely to interfere with completion of the rehabilitation program or scheduled follow-up were also excluded, as were pregnant women and individuals participating in another interventional study.

Eligible patients who satisfied the predefined criteria and consented to participation underwent baseline clinical and physiological assessment before randomization. A total sample of 100 participants was enrolled. The sample size was estimated using G*Power version 3.1 on the basis of an anticipated moderate between-group effect size of Cohen's $d = 0.60$ for improvement in CFR, with 80% statistical power and a two-sided alpha level of 0.05. The estimated minimum requirement was 45 participants per group. To allow for an anticipated attrition rate of approximately 10%, the final enrollment target was increased to 50 participants per group, giving a total planned sample of 100.

Participants were randomly assigned to either the tailored exercise group or the standard cardiac rehabilitation group using a computer-generated random allocation sequence. The sequence was managed by an independent research coordinator to maintain allocation concealment during enrollment and assignment. Both groups underwent baseline assessment that included medical history, anthropometric evaluation, echocardiography, cardiopulmonary exercise testing, assessment of coronary microvascular function, peripheral endothelial function, biochemical markers, and health-related quality of life. Cardiopulmonary exercise testing was used to determine peak oxygen uptake ($VO_{2\text{peak}}$) and characterize baseline exercise capacity. Left ventricular systolic function was assessed by echocardiography, while coronary microvascular function was evaluated using CFR and IMR. Invasive physiological measurements were obtained using a pressure–temperature sensor-tipped coronary guidewire. Non-invasive assessment of coronary flow reserve using transthoracic Doppler echocardiography was also incorporated as part of the physiological evaluation. Peripheral endothelial function was assessed through brachial artery flow-mediated dilation (FMD). Blood samples were used to assess endothelial and inflammatory biomarkers, including nitric oxide, endothelin-1, and high-sensitivity C-reactive protein (hs-CRP).

Participants allocated to the tailored exercise group undertook a supervised, individualized exercise program developed according to baseline cardiopulmonary exercise capacity and coronary physiological findings. The program incorporated aerobic exercise using a treadmill, cycle ergometer, or brisk walking three times per week. Aerobic intensity was prescribed at approximately 60–80% of the participant's measured $VO_{2\text{peak}}$ and was progressively modified according to exercise tolerance and reassessment of functional capacity. Participants additionally performed resistance exercise targeting the major muscle groups twice weekly at approximately 50–60% of one-repetition maximum. Exercise prescriptions were reviewed during scheduled reassessments and modified according to physiological response, functional progression, and tolerance. In addition to supervised exercise, participants received counseling regarding habitual physical activity, dietary optimization, and stress management. Exercise adherence and training exposure were monitored using attendance records and wearable heart-rate monitoring during supervised sessions.

Participants randomized to the standard cardiac rehabilitation group received the institutional rehabilitation program comprising moderate-intensity aerobic exercise, predominantly walking or stationary cycling, three times per week for approximately 40 minutes per session. Exercise intensity was delivered according to the standard institutional approach without individualized adjustment based on microvascular indices and without the additional resistance-training component used in the tailored program. Both groups continued guideline-directed medical

treatment prescribed by their cardiologists throughout the study. Relevant therapy included antiplatelet agents, statins, beta-blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers where clinically indicated. Adverse events occurring during rehabilitation or follow-up were documented throughout the study period.

Study assessments were performed at baseline, 6 months, and 12 months. The primary outcome was change in CFR from baseline to 12 months. IMR was evaluated as an additional measure of coronary microvascular resistance. Secondary outcomes included change in VO_2peak , brachial artery FMD, circulating nitric oxide, endothelin-1 and hs-CRP concentrations, and health-related quality of life. Quality of life was assessed using the MacNew Heart Disease Health-Related Quality of Life questionnaire, which evaluates physical, emotional, and social domains. Physiological and functional assessments were conducted using standardized procedures at the scheduled study time points, and the same outcome definitions were applied to both treatment groups to reduce differential measurement.

Data were analyzed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean $\pm$ standard deviation and categorical variables as frequencies and percentages. Distributional assumptions for continuous variables were evaluated using the Shapiro-Wilk test. Baseline between-group comparisons were performed using independent-samples *t* tests for continuous variables and chi-square tests for categorical variables, as appropriate. Longitudinal changes in CFR, IMR, and VO_2peak were evaluated using repeated-measures analysis of variance to assess changes over time and differences between treatment groups. Where post-hoc pairwise comparisons were undertaken, the Bonferroni procedure was applied to control for multiple comparisons. Secondary physiological, endothelial, biochemical, and quality-of-life outcomes were compared between groups according to the corresponding measurement time points. All statistical tests were two-sided, and a *p* value <0.05 was considered statistically significant.

The principal analyses were conducted according to the intention-to-treat principle, with participants analyzed according to their original randomized allocation. Missing observations were addressed using multiple imputation to reduce potential bias associated with incomplete follow-up data. Exercise attendance records, wearable heart-rate monitoring, predefined eligibility criteria, standardized outcome definitions, and uniform follow-up schedules were used to support intervention fidelity and consistency of data collection. Confidentiality was maintained through coded participant identifiers, and study records were stored securely with access restricted to authorized research personnel. Participants who discontinued the assigned intervention remained eligible for follow-up and were offered routine cardiac rehabilitation care through the hospital service.

RESULTS

A total of 100 participants were randomized equally to the tailored exercise and standard cardiac rehabilitation groups. Baseline demographic and clinical characteristics were comparable between groups (Table 1). Mean age was 61.4 ± 8.6 years in the tailored exercise group and 60.8 ± 8.9 years in the standard rehabilitation group ($p=0.732$). Men comprised 74.0% and 72.0% of the respective groups. No statistically significant baseline differences were observed in BMI, hypertension, diabetes mellitus, current smoking, LVEF, beta-blocker use, or ACE inhibitor/ARB use.

Coronary microvascular function improved in both groups over 12 months, with larger changes in the tailored exercise group (Table 2). CFR increased from 2.08 ± 0.21 to 2.84 ± 0.26 in the tailored group and from 2.09 ± 0.23 to 2.45 ± 0.29 in the standard rehabilitation group. The mean increase in CFR was $+0.76 \pm 0.24$ versus $+0.36 \pm 0.22$, corresponding to a between-group difference in change of $+0.40$ (95% CI 0.31 to 0.49; $p<0.001$; Cohen's $d=1.74$). IMR decreased from 31.6 ± 5.4 to 23.1 ± 4.8 in the tailored group and from 31.8 ± 5.6 to 27.2 ± 5.2 in the standard rehabilitation group. The corresponding changes were -8.5 ± 3.7 and -4.6 ± 3.1 , yielding a difference between-group difference in change of -3.90 units (95% CI -5.26 to -2.54 ; $p<0.001$; Cohen's $d=-1.14$). Functional capacity and vascular outcomes also differed between groups at 12 months (Table 3). VO_2peak increased by 7.4 mL/kg/min in the tailored exercise group compared with 4.2 mL/kg/min in the standard rehabilitation group. At 12 months, the between-group difference in VO_2peak was 3.30 mL/kg/min (95% CI 1.87 to 4.73; $p<0.001$; $d=0.92$). FMD increased by 3.7 percentage points in the tailored group and 2.0 percentage points in the standard rehabilitation group, with a 12-month between-group difference of 1.80 percentage points (95% CI 1.38 to 2.22; $p<0.001$; $d=1.71$).

Table 1. Baseline Demographic and Clinical Characteristics of Randomized Participants (N = 100)

Variable	Tailored Exercise (n = 50)	Standard Rehabilitation (n = 50)	p-value
Age, years	61.4 ± 8.6	60.8 ± 8.9	0.732
Male sex, n (%)	37 (74.0)	36 (72.0)	0.822
BMI, kg/m ²	27.6 ± 3.1	27.9 ± 3.3	0.640
Hypertension, n (%)	28 (56.0)	29 (58.0)	0.840
Diabetes mellitus, n (%)	24 (48.0)	23 (46.0)	0.841
Current smoking, n (%)	21 (42.0)	22 (44.0)	0.840
LVEF, %	57.8 ± 6.2	56.9 ± 6.1	0.466
Statin use, n (%)	50 (100.0)	50 (100.0)	—
Beta-blocker use, n (%)	46 (92.0)	45 (90.0)	0.727
ACE inhibitor/ARB use, n (%)	44 (88.0)	43 (86.0)	0.766

Continuous variables are presented as mean ± SD and categorical variables as n (%). P-values for continuous variables were calculated using independent-samples t tests. P-values for categorical variables were calculated using Pearson chi-square tests. BMI, body mass index; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 2. Change in Coronary Microvascular Function From Baseline to 12 Months

Outcome	Tailored Exercise (n = 50)	Standard Rehabilitation (n = 50)	Between-group difference in change (95% CI)	p-value	Cohen's d
CFR, baseline	2.08 ± 0.21	2.09 ± 0.23	—	—	—
CFR, 12 months	2.84 ± 0.26	2.45 ± 0.29	—	—	—
CFR change	+0.76 ± 0.24	+0.36 ± 0.22	+0.40 (0.31 to 0.49)	<0.001	1.74
IMR, baseline	31.6 ± 5.4	31.8 ± 5.6	—	—	—
IMR, 12 months	23.1 ± 4.8	27.2 ± 5.2	—	—	—
IMR change	−8.5 ± 3.7	−4.6 ± 3.1	−3.90 (−5.26 to −2.54)	<0.001	−1.14

Values are mean ± SD. Between-group differences compare mean change scores between treatment groups. CFR, coronary flow reserve; IMR, index of microcirculatory resistance; CI, confidence interval.

Table 3. Functional Capacity, Endothelial Function, and Biochemical Outcomes

Outcome	Tailored Exercise Baseline	Tailored Exercise 12 Months	Change	Standard Rehabilitation Baseline	Standard Rehabilitation 12 Months	Change	12-month between-group difference (95% CI)	p-value	Cohen's d
VO ₂ peak, mL/kg/min	18.2 ± 3.1	25.6 ± 3.7	+7.4	18.1 ± 3.0	22.3 ± 3.5	+4.2	+3.30 (1.87 to 4.73)	<0.001	0.92
FMD, %	4.1 ± 0.8	7.8 ± 1.1	+3.7	4.0 ± 0.9	6.0 ± 1.0	+2.0	+1.80 (1.38 to 2.22)	<0.001	1.71
hs-CRP, mg/L	3.9 ± 1.2	2.1 ± 0.9	−1.8	3.8 ± 1.3	2.9 ± 1.0	−0.9	−0.80 (−1.18 to −0.42)	<0.001	−0.84
Nitric oxide, μmol/L	38.5 ± 6.7	52.9 ± 8.1	+14.4	38.2 ± 7.0	46.4 ± 7.9	+8.2	+6.50 (3.32 to 9.68)	<0.001	0.81

Values are mean ± SD except change values, which represent differences between reported baseline and 12-month means. Between-group differences and 95% CIs were calculated from the reported 12-month group means and SDs. VO₂peak, peak oxygen uptake; FMD, flow-mediated dilation; hs-CRP, high-sensitivity C-reactive protein; CI, confidence interval.

Table 4. Health-Related Quality-of-Life Outcomes at Baseline and 12 Months

MacNew domain	Tailored Exercise Baseline	Tailored Exercise 12 Months	Change	Standard Rehabilitation Baseline	Standard Rehabilitation 12 Months	Change	12-month between-group difference (95% CI)	p-value	Cohen's d
Physical	4.2 ± 0.7	6.7 ± 0.8	+2.5	4.1 ± 0.6	5.8 ± 0.9	+1.7	+0.90 (0.56 to 1.24)	<0.001	1.06
Emotional	4.6 ± 0.8	6.8 ± 0.7	+2.2	4.5 ± 0.9	5.9 ± 0.8	+1.4	+0.90 (0.60 to 1.20)	<0.001	1.20

Values are mean ± SD. Change values represent differences between the reported baseline and 12-month means. Between-group differences and 95% CIs were calculated from the reported 12-month means and SDs. CI, confidence interval. Biochemical outcomes showed a similar pattern. Mean hs-CRP declined from 3.9 ± 1.2 to 2.1 ± 0.9 mg/L in the tailored exercise group and from 3.8 ± 1.3 to 2.9 ± 1.0 mg/L in the standard rehabilitation group. The 12-month between-group difference was −0.80 mg/L (95% CI −1.18 to −0.42; p<0.001; d=−0.84). Nitric oxide increased by 14.4 μmol/L in the tailored group and 8.2 μmol/L in the standard rehabilitation group, producing a 12-month between-group difference of 6.50 μmol/L (95% CI 3.32 to 9.68; p<0.001; d=0.81).

Health-related quality of life increased in both treatment groups (Table 4). The MacNew physical-domain score increased by 2.5 points in the tailored exercise group and by 1.7 points in the standard rehabilitation group. At 12 months, the tailored group had a 0.90-point higher physical-domain score (95% CI 0.56 to 1.24; p<0.001; d=1.06). Emotional-domain scores increased by 2.2 and 1.4 points, respectively, with a corresponding between-group

difference of 0.90 points at 12 months (95% CI 0.60 to 1.20; $p < 0.001$; $d = 1.20$). No major adverse events or exercise-related complications were reported during the study.

DISCUSSION

The present randomized trial found that a tailored exercise program was associated with greater improvement in coronary microvascular function than standard cardiac rehabilitation among patients with documented coronary microvascular dysfunction after PCI. The principal finding was a larger increase in CFR accompanied by a greater reduction in IMR in the tailored exercise group. Improvements in exercise capacity, peripheral endothelial function, inflammatory and endothelial biomarkers, and health-related quality of life were also more pronounced in the tailored group. Taken together, these findings suggest that a more individualized and progressively adjusted rehabilitation strategy may provide additional physiological benefit beyond a conventional aerobic rehabilitation program in this selected post-PCI population.

The observed improvement in coronary microvascular indices is clinically relevant because persistent symptoms after technically successful PCI may arise from mechanisms not corrected by restoration of epicardial vessel patency alone. Residual angina and functional limitation after PCI have increasingly been recognized as multifactorial, with coronary microvascular abnormalities representing one potential contributor (1). Similarly, physiological assessment of the coronary microcirculation after PCI has been shown to provide prognostic information beyond conventional angiographic assessment, supporting the importance of evaluating microvascular recovery rather than relying exclusively on epicardial procedural success (3). In this context, the greater improvement in CFR and reduction in IMR observed in the tailored exercise group are consistent with the broader concept that post-PCI management may benefit from attention to residual physiological abnormalities.

The findings also support the potential value of individualized physiological assessment in guiding post-PCI management. Contemporary interventional research has increasingly emphasized treatment strategies informed by physiological characteristics rather than angiographic appearance alone, including approaches that use coronary functional assessment to guide therapeutic decision-making (4,5). Although those studies addressed PCI decision-making rather than exercise rehabilitation, the underlying principle of matching treatment intensity to patient-specific physiological characteristics is relevant to the present intervention. In this trial, exercise intensity and progression were informed by baseline exercise capacity and coronary physiological findings, which may have allowed the intervention to better accommodate differences in functional reserve and treatment tolerance between participants.

Several biological mechanisms may plausibly contribute to the observed pattern of microvascular and endothelial improvement. Repeated aerobic exercise increases blood-flow-related shear stress and may promote endothelial adaptation, improved vasodilatory responsiveness, and greater nitric oxide availability. The larger increase in circulating nitric oxide and greater improvement in brachial artery FMD in the tailored group are compatible with improved systemic endothelial function. The concurrent reduction in hs-CRP is also consistent with a reduction in systemic inflammatory activity. These findings should, however, be interpreted as supportive physiological associations rather than proof that changes in nitric oxide or inflammation directly mediated the improvement in coronary microvascular function, because formal mediation analysis was not performed.

The increase in VO_{2peak} further indicates that the tailored program was associated with greater improvement in cardiorespiratory fitness. This difference may reflect individualized aerobic intensity, progressive modification of exercise load, and the addition of resistance training. Importantly, the intervention differed from standard rehabilitation in several respects beyond personalization alone. Participants in the tailored group received resistance exercise, more individualized progression, and additional counseling regarding physical activity, diet, and stress management. Consequently, the trial demonstrates the effect of a more comprehensive, individualized rehabilitation package rather than isolating the independent effect of physiological tailoring. The observed between-group differences therefore cannot be attributed exclusively to the use of CFR, IMR, or CPET-based personalization.

Improvements in health-related quality of life were also greater in the tailored group for the physical and emotional domains that could be evaluated reliably from the reported data. These changes are compatible with the parallel gains in exercise capacity and vascular function and may reflect improved functional confidence and symptom

tolerance during recovery. Persistent symptoms after PCI can substantially affect patients' perceived health status even when epicardial revascularization has been technically successful, emphasizing the importance of patient-reported outcomes alongside physiological endpoints (1). Nevertheless, quality-of-life findings should be interpreted in conjunction with the physiological outcomes rather than as independent evidence of long-term clinical benefit.

The study has several strengths. Its randomized, parallel-group design reduced the likelihood that baseline differences alone explained the observed treatment effects. The evaluation combined invasive coronary physiological indices with functional, endothelial, biochemical, and patient-reported outcomes, providing a multidimensional assessment of recovery. The 12-month follow-up period also permitted evaluation beyond the immediate post-PCI rehabilitation phase. In addition, the use of CFR and IMR allowed the study to address coronary microvascular function directly rather than relying solely on exercise performance or symptoms, which is particularly relevant given the prognostic significance of post-PCI microcirculatory abnormalities (3).

Several limitations should also be considered. The study was performed at a single tertiary care center with a relatively modest sample size, limiting generalizability to broader post-PCI populations. Eligibility required documented microvascular dysfunction and preserved or mildly impaired left ventricular systolic function; consequently, the findings may not apply to patients without CMD, those with advanced heart failure, or patients unable to participate in supervised exercise. Participant and therapist blinding was inherently difficult in an exercise trial, and the available study description does not establish whether outcome assessors or analysts were blinded. The intervention and control groups were not matched for all rehabilitation components, particularly resistance training and lifestyle counseling, which limits attribution of the observed effect specifically to individualized exercise prescription. In addition, multiple physiological and biochemical secondary outcomes were evaluated, increasing the possibility of chance findings despite correction for selected comparisons.

The analysis is also limited by the absence of reported 6-month outcome data despite planned assessment at baseline, 6 months, and 12 months, which restricts interpretation of the trajectory of treatment response. Detailed adherence and exercise-dose data were not presented, preventing assessment of whether differences in training exposure contributed to the observed outcomes. Changes in concomitant cardiovascular medications and other lifestyle factors during follow-up could also have influenced endothelial and inflammatory measures. Furthermore, the study was not designed or powered to determine effects on major clinical outcomes such as recurrent myocardial infarction, hospitalization, repeat revascularization, or mortality. The findings therefore support physiological and functional benefit but should not be interpreted as evidence of reduced long-term cardiovascular events.

Overall, the findings suggest that a comprehensive, individualized rehabilitation strategy may provide greater improvement in coronary microvascular physiology and functional recovery than a conventional aerobic rehabilitation program in selected patients with CMD after PCI. Confirmation in larger multicenter trials with clearly standardized intervention components, complete longitudinal reporting, detailed adherence assessment, and clinically important cardiovascular endpoints would be necessary to determine the broader applicability and long-term clinical significance of this approach.

CONCLUSION

Among post-PCI patients with documented coronary microvascular dysfunction, the tailored rehabilitation program was associated with greater improvement in CFR, IMR, exercise capacity, endothelial function, selected biochemical markers, and health-related quality of life than standard cardiac rehabilitation over 12 months. These findings support the potential value of individualized, progressively adjusted rehabilitation for enhancing physiological and functional recovery after PCI, while the additional intervention components and single-center design warrant cautious interpretation of the magnitude and generalizability of the observed benefit.

REFERENCES

1. Hamana T, Grogan A, Kawakami R, Virmani R, Finn AV. Calcified nodules: pathology, mechanisms, and clinical challenges. *Curr Cardiol Rep.* 2025;27(1):140.

2. Reddy RK, Bernstein H, Howard JP, Ahmad Y. Complete revascularization with percutaneous coronary intervention for acute coronary syndromes presenting with multivessel disease. *Curr Opin Cardiol*. 2025;40(6):410-6.
3. Fezzi S, Scheller B, Rissanen TT, Malivojevic R, Tavella D, Lunardi M, et al. Drug-coated balloons for coronary bifurcation lesions. *EuroIntervention*. 2025;21(20).
4. Maqsood MH, Zhang RS, Rawal N, Sella G, Kleiman NS, Bangalore S. Drug-eluting stent, drug-coated balloon, or plain old balloon angioplasty for in-stent coronary restenosis: insights from a mixed treatment comparison meta-analysis of randomized trials. *Circ Cardiovasc Interv*. 2025;18(12).
5. Tarantini G, Honton B, Paradies V, Lemesle G, Range G, Godin M, et al. Early discontinuation of aspirin after PCI in low-risk acute myocardial infarction. *N Engl J Med*. 2025;393(21):2083-94.
6. Leite L, Carlos T, Ferraz Costa G, Cruz I, Donato H, Silva R, et al. Effect of percutaneous coronary intervention on chronic total occlusions with documented viability or ischemia: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2025;26(1):17.
7. Ali ZA, Spratt JC, Finn AV, Maehara A, Shin D. Identification and treatment of calcified nodules in percutaneous coronary intervention. *EuroIntervention*. 2025;21(23).
8. Landi A, Karaboue MA, De Luca L. Improving on current guidelines for aspirin-free strategies after percutaneous coronary intervention and future perspectives. *Expert Rev Cardiovasc Ther*. 2025;23(12):821-9.
9. Fezzi S, Serruys PW, Cortese B, Scheller B, Alfonso F, Jeger R, et al. Indications for use of drug-coated balloons in coronary intervention: Academic Research Consortium position statement. *J Am Coll Cardiol*. 2025;86(15):1170-202.
10. Ali ZA, Volleberg R, Shin D, Chong L, Calistro C, Ansari A, et al. Intravascular imaging in chronic total occlusion percutaneous coronary intervention. *Interv Cardiol Clin*. 2026;15(1):111-20.
11. Khan SU, Kleiman NS, Shah AR. Intravascular ultrasound imaging-guided percutaneous coronary intervention: evidence and practical implications. *Methodist Debakey Cardiovasc J*. 2025;21(4):26-36.
12. Sedghi A, von Rennenberg R, Petzold G, Nickenig G, Kallmünzer B, Achenbach S, et al. Intravenous thrombolysis before percutaneous coronary intervention in patients with non-ST-elevation acute coronary syndrome and acute ischaemic stroke: a subanalysis of the PRAISE study. *Open Heart*. 2025;12(2).
13. Kladou E, Strepkos D, Alexandrou M, Mutlu D, Carvalho PEP, Sara JDS, et al. Modification procedures for chronic total occlusion percutaneous coronary intervention: insights from the PROGRESS-CTO Registry. *Catheter Cardiovasc Interv*. 2025;106(7):3628-39.
14. Fretz T, Dasari S, Sakaleros J, Kayani AMA, Bluckner N, Pond K, et al. One-year outcomes of short-term dual antiplatelet therapy following percutaneous coronary intervention with drug-eluting stents: a meta-analysis of randomized clinical trials. *Catheter Cardiovasc Interv*. 2025;106(6):3286-96.
15. Jalli S, Strepkos D, Alexandrou M, Mutlu D, Carvalho PEP, Kladou E, et al. Optimal approach in staged chronic total occlusion percutaneous coronary intervention. *Curr Cardiol Rep*. 2025;27(1):151.
16. Marquard JM, Beske RP, Hassager C, Jensen LO, Eiskjær H, Mangner N, et al. Percutaneous coronary intervention in multivessel disease and infarct-related cardiogenic shock: a DanGer Shock substudy. *JACC Cardiovasc Interv*. 2025;18(18):2226-37.
17. Čanković M, Preveden A, Ivanović V, Milovančev A, Petrović M, Kovačević M, et al. Percutaneous coronary intervention on saphenous vein graft in second-generation drug-eluting stent era. *Acta Clin Croat*. 2024;63(3-4):611-8.
18. Li C, Zhou Y, Lu D, Ma J, Dai C, Ma J, et al. Periprocedural assessment of coronary microcirculatory function to predict clinical outcomes after elective percutaneous coronary intervention. *J Am Heart Assoc*. 2025;14(19).

19. D'Ascenzo F, Caranzano I, De Filippo O, Giacobbe F, Leone AM, Sanavia T, et al. Phenomapping-derived selection of fractional flow reserve or optical coherence tomography to personalise percutaneous coronary intervention. *Open Heart*. 2025;12(2).
20. Yoshimachi F, Yamaji K, Kohsaka S, Kawamura Y, Kasai S, Fujii T, et al. Procedural characteristics and safety of slender percutaneous coronary intervention: slender is better. *Catheter Cardiovasc Interv*. 2025;106(5):2844-9.
21. Xu T, Lin S, Liu S, Xu H, Bai X, Zhou X, et al. Risk factors of nosocomial infection after percutaneous coronary intervention: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2025;25(1):832.
22. Chotai S, Chiew K, Al-Lamee R. Symptoms, coronary artery disease and percutaneous coronary intervention: connecting the dots. *Curr Opin Cardiol*. 2025;40(6):417-23.
23. Yin F, Zhang Y, Zhang X, Chen Y, Cui X. Updated meta-analysis of fractional flow reserve versus coronary angiography for guiding percutaneous coronary intervention. *PLoS One*. 2025;20(10).