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Cardiac Rehabilitation Improves Endothelial Function in Coronary Artery Disease Patients

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ABSTRACT

Exercise-based cardiac rehabilitation may be an effective non-pharmacological intervention for improving endothelial function in coronary artery disease patients. Therefore, this systematic review with meta-analysis aimed to (a) estimate the training-induced effect on endothelial and vascular smooth muscle function, assessed by flow-mediated dilation and nitroglycerin-mediated dilation, respectively, in coronary artery disease patients; and to (b) study the influence of potential trial-level variables (i. e. study and intervention characteristics) on the training-induced effect on endothelial and vascular smooth muscle function. Electronic searches were performed in Pubmed, Scopus, and Embase up to February 2021. Random-effects models of standardised mean change were estimated. Heterogeneity analyses were performed by using the Chi^2 test and I^2 index. Our results showed that exercise-based cardiac rehabilitation significantly enhanced flow-mediated dilation (1.04 [95 % confidence interval = 0.76 to 1.31]) but did not significantly change nitroglycerin-mediated dilation (0.05 [95 % confidence interval = –0.03 to 0.13]). Heterogeneity testing reached statistical significance ($p < .001$) with high inconsistency for flow-mediated dilation ($I^2 = 92$ %). Nevertheless, none of the analysed variables influenced the training-induced effect on flow-mediated dilation. Exercise-based cardiac rehabilitation seems to be an effective therapeutic strategy for improving endothelial-dependent dilation in coronary artery disease patients, which may aid in the prevention of cardiovascular events.

Introduction

Endothelial dysfunction is one of the leading factors in the pathogenesis of atherosclerosis, contributing to the development and progression of coronary artery disease (CAD) [1]. It is associated with impaired exercise capacity and increased risk of mortality in cardiac patients [2–4]. Endothelial dysfunction is characterised by a decrease in the bioavailability of vasodilators, particularly nitric oxide (NO) bioavailability (i. e. decreased NO production and/or increased NO degradation by reactive oxygen species) and/or hyporesponsiveness of vascular smooth muscle and/or an increase in en-

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dothelium-derived contracting factors [5, 6]. Disruption of this delicate balance between vasodilators and vasoconstrictors leads to an impairment of endothelium-dependent dilation.

Endothelial function can be assessed on a daily basis using a flow-mediated dilation (FMD) technique. FMD represents an endothelium-dependent dilation, mainly mediated by NO, in response to oxygen debt due to the interruption of blood flow and is the most common method used for noninvasively assessing endothelial function in peripheral conduit arteries (i. e. brachial, radial, and femoral) [7]. This technique provokes vasodilation in response to an imposed increase in blood flow and shear stress induced by reactive hyperaemia [8, 9]. Vasodilation in response to reactive hyperaemia is an endothelium-dependent NO-mediated phenomenon [10], which has been confirmed by studies that used N-monomethyl arginine, a selective blockade of NO production which abolishes vasodilation [11]. FMD is inversely associated with cardiovascular events [12], and persistent impairment in FMD independently predicts cardiovascular events in patients with CAD and chronic heart failure (CHF) [13, 14]. Despite its widespread use, several methodological issues such as analysis used (i. e. automatic or manual), cuff position (i. e. distal or proximal to the ultrasound probe), and occlusion duration or time of peak measurement diameter after cuff release, might impact the reproducibility of FMD measurements and the comparison of the results with previous studies [15–17]. In combination with FMD, endothelium-independent nitroglycerin-mediated dilation (NMD) is also measured via the exogenous administration of NO to assess vascular smooth muscle function [16], which might contribute to the observed FMD changes.

Ample evidence shows that physical exercise is a non-pharmacological treatment capable of restoring and ameliorating peripheral endothelial function, assessed by FMD, in healthy people and clinical populations [18–21]. However, the effect of exercise-based cardiac rehabilitation (CR) on endothelium-independent dilation, assessed by NMD, seems to be more limited [22]. The improvement of antioxidant status (i. e. increasing NO bioavailability) and inflammatory biomarkers (i. e. C-reactive protein and cytokines), as well as the endothelial repair/regeneration (i. e. mobilisation of bone marrow-derived endothelial progenitor cells [EPCs]) have been proposed as potential mechanisms underlying the training-induced effect on endothelium-dependent dilation [23–25]. Lanza et al. [26] recently reported in a narrative review that exercise-based CR based on aerobic training (AT) improves endothelium-dependent dilation in patients with CAD or CHF. Authors hypothesised that reduced turbulent flow may partly explain the beneficial effects of AT on endothelial dysfunction. However, limited research prevents definitive conclusions on the influence of different training methods (i. e. AT, resistance training [RT], and combined AT and RT [CT]), and training characteristics (i. e. frequency, intensity, type, and time) on the training-induced effect on endothelial function. In this regard, ischaemia is a powerful stimulus for mobilisation of EPCs, mainly due to the release of angiogenic factors (i. e. vascular endothelial growth factors and hypoxia-inducible factor 1). RT is characterised by repeated periods of muscular contraction leading to intermittent bouts of hypoxia, which could induce a higher release of angiogenic factors and mobilise EPCs. For instance, Ribeiro et al. [27] investigated the acute effect of RT at different intensities on the mobilisation of EPCs and reported significantly higher concentrations of angiogenic factors and EPCs after a single bout of RT compared to baseline, as well as a dose-response relationship between exercise intensity and EPC mobilisation.

Great clarity regarding the effect of exercise modalities and methodological factors on endothelial function is required. Therefore, the current systematic review with meta-analysis aimed to determine the effects of exercise-based CR on endothelial and vascular smooth muscle function, assessed noninvasively via FMD and NMD in peripheral arteries, respectively, in CAD patients. A secondary aim was to test the influence of potential moderator characteristics on the effect of exercise-based CR on endothelial and vascular smooth muscle function. Based on previous evidence obtained from patients with other pathologies, we hypothesised that exercise-based CR would be suitable for improving endothelium-dependent dilation in CAD patients, whereas the effect of exercise-based CR on endothelium-independent dilation would be less pronounced. We also hypothesised that the effect of exercise-based CR on endothelial function would be influenced by potential moderator variables (i. e. study and training characteristics).

Materials and Methods

The present study was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [28]. The systematic review with meta-analysis protocol was prospectively registered on the PROSPERO database (CRD42021237593).

Data search and sources

Electronic searches were carried out in Pubmed, Scopus, and Embase from inception to February 2021 using free-text terms based on the PIO (participants, intervention, and outcomes) strategy. Language restrictions were not applied during this phase and the electronic search of each individual database was adapted as necessary (the full search strategy can be found in the **Supplementary Material, Appendix 1**). Conference proceedings were also searched on the Web of Science Core Collection. We also conducted manual searches of reference lists from all included studies and previous reviews to identify additional potentially eligible studies. Finally, authors of selected studies were contacted in an attempt to identify unpublished or ongoing studies that fulfilled our selection criteria.

Study selection

Eligibility criteria were established according to the PICOS (participants, intervention, comparisons, outcomes, and study design) guideline, and study selection was performed using the following inclusion criteria: (participants) studies that enrolled adult patients (≥ 18 years), regardless of sex, who had experienced an acute coronary syndrome, who had undergone revascularisation (i. e. percutaneous transluminal intervention or coronary artery bypass grafting), or who had a diagnosis of CAD documented by angiography; (intervention) supervised interventions, home-based interventions, or mixed supervised and home-based interventions based on AT, RT or CT, either alone or in addition to psychosocial and/or educational interventions; (study design and comparisons) non-controlled studies

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(i. e. single intervention, randomised, and non-randomised studies), as well as randomised and non-randomised controlled studies, where control group (CG) could include usual care and psychosocial and/or educational interventions but not a structured exercise training program. Non-controlled and non-randomised studies were included to analyse the impact of the study design on the results of previous studies; (outcomes) endothelial and vascular smooth muscle function, assessed noninvasively via FMD and NMD, respectively, in peripheral conduit arteries (e. g. brachial and femoral). Moreover, studies written in English, Spanish, or Portuguese could be included, and the selection of studies with more than one article based on the same sample was limited to only one.

Two authors (A.C. and A.M.) assessed all identified titles/abstracts for possible inclusion. When lack of consensus arose, the article was included in the next stage. The same authors reviewed the full texts against the inclusion criteria, and disagreements were settled by consensus. If consensus was not achieved, a third author (J.M.S.) assessed the study to obtain agreement.

Data extraction, coding study characteristics, and potential moderator variables

Two authors (A.M. and A.C.) coded the characteristics of the included studies using a standardised data extraction form. In cases of uncertainty, a third author (F.R.) assessed the study to obtain agreement.

The following information was extracted from the included studies: (a) study characteristics (publication year, country, study design [i. e. single intervention study, non-randomised study, randomised study, non-randomised controlled study, and randomised controlled study], and journal); (b) baseline patient characteristics according to allocated group (sample size, mean percentage, age, body mass index, left ventricular ejection fraction, and cardiorespiratory fitness (CRF) [i. e. peak oxygen uptake and metabolic equivalent of task]); (c) intervention characteristics (setting [i. e. supervised, home-based, or mixed], lifestyle program [i. e. exercise only or multicomponent], intervention length [in weeks], training method [i. e. AT, RT, or CT], AT intensity [if applicable] [i. e. moderate intensity training (MIT) or high intensity interval training (HIIT)], training frequency [in sessions a week], intensity [i. e. oxygen uptake percentage and percentage of one-repetition maximum (1RM)], and volume [i. e. session length, sets, number of repetitions, and interval length]); (d) FMD assessment characteristics (artery measured, cuff placement [i. e. distal or proximal to the imaged artery], occlusion length [in seconds], occlusion pressure [in mmHg], post-occlusion assessment length [in seconds], and analysis [i. e. automated, semi-automated, or manual]); (e) NMD assessment characteristics (artery measured, baseline diameter [in mm], via administration [i. e. sublingual administration or intra-arterial infusion], dose [in mg], and post-administration assessment length [in seconds]); and (f) mean ± standard deviation (*SD*) or median and range or interquartile range of FMD and/or NMD before and after the intervention period. For articles that did not report training/patient characteristics and/or outcome data (e. g. mean and *SD*), authors were contacted for this information via e-mail. If a response was not received, the article was excluded from the qualitative or quantitative synthesis, respectively.

Assessment of risk of bias

Two reviewers (A.M. and J.M.S.) independently assessed systematic risk of bias of each study included in our meta-analyses. Disagreements between both reviewers were settled by consensus. The RoB 2 tool (revised tool for risk of bias in randomised studies) and the ROBINS-I tool (risk of bias in non-randomised studies of interventions) were used for assessing randomised and non-randomised studies, respectively [29]. Risk of bias assessment was carried out based on the descriptive judgements proposed in the Cochrane Handbook [29].

Computation of effect size and statistical analyses

The standardised mean change (SMC) was used as the effect size (ES) index for estimating within-group FMD and/or NMD changes in the experimental group (EG). Therefore, the analysis unit in this meta-analysis was the group. Despite internal validity of within-group ESs being lower than interval validity of between-group ESs, the use of within-group ESs is recommended when there are many non-controlled studies [30, 31], allowing us to increase the number of studies to carry out moderator analyses. The SMC was calculated by subtracting the pre-intervention mean value from the post-intervention mean value divided by the *SD* at pre-intervention, and then corrected by a factor for small samples [32–34]. In studies reporting data as median and range or interquartile range, the means ± *SD*s were estimated using the formula proposed by Wan et al. [35]. Separate meta-analyses were performed for each SMC index according to the outcome measure to avoid statistical dependence. A random effects model was applied for each meta-analysis in which the weighting factor was the inverse variance, defined as the sum of the within-study and the between-study variance [36].

The analysis comprised calculating the mean ES with its 95 % confidence interval (CI), a heterogeneity statistical test, chi-square, and the I^2 index to evaluate the degree of homogeneity of the ESs around the average effect [37, 38]. The magnitude of SMC was classified as trivial (< 0.2), small (0.2 to 0.6), moderate (0.61 to 1.2), large (1.21 to 2.0) or very large (> 2.0) [39], and the ESs were considered statistically significant when $p \leq .050$. Heterogeneity I^2 index values were classified as low, moderate, or high at 25 %, 50 %, and 75 %, respectively. Heterogeneity values greater than 50 % indicated substantial heterogeneity [40]. If substantial heterogeneity was found, heterogeneity analyses were carried out by analysing the relationship between the ESs and the categorical (i. e. study design [randomised vs. non-randomised], setting, lifestyle program, training method, and AT intensity) and continuous moderator variables (i. e. publication year, sample size, mean percentage, intervention length, training frequency, and number of sessions) using subgroup analyses and simple meta-regressions (coefficient *B*, with 95 % CI), respectively. All analyses were performed using weighted least squares and assuming mixed-effect models [41]. For subgroup analyses, at least three analysis units must have investigated a moderator sublevel to test its effects, whereas meta-regressions were carried out when a minimum of 10 analysis units reported the specific continuous covariate.

Publication bias analyses were performed using funnel plots. The non-parametric trim-and-fill method was used for imputing missed ESs [42, 43]. Publication bias analyses were performed when there were at least 10 studies included in the meta-analysis [31].

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Sensitivity analyses were carried out to test the robustness of our findings. We analysed the effect of including those studies that reported data as median and range or interquartile range, as well as of including/excluding each individual analysis. Pooled analyses were also performed by calculating the standardised mean difference (SMD) in controlled studies. The SMD was calculated by subtracting the mean change in the CG from the mean change in the EG divided by the pooled *SD* at baseline. In multi-intervention studies with one shared CG, the sample size of the CG was split up by the number of EGs to avoid overinflation of the sample size [44]. Finally, we also estimated the mean difference (MD), which was defined as the difference of the mean change between the two groups (EG and CG), for knowing the impact of the ES index used (i. e. standardised vs. non-standardised) and allowing clinicians to more easily interpret the results. It should be noted that the decision to perform this analysis was made after extracting study information as all included studies reported FMD and/or NMD as percent changes. All analyses were performed using STATA software (version 16.0; Stata Corp LLC, College Station, TX, USA).

Results

Description of selected studies

The results of our study selection process are depicted in ▶ **Fig. 1**. In brief, the electronic database search retrieved 1408 studies after deleting duplicates, while the manual search of the reference lists of the included studies and previous reviews retrieved one study. After reviewing titles and abstracts, 32 studies were eligible for full text analysis, of which 11 were excluded from the systematic review for the following reasons: writing in another language (n = 2), included patients with other pathologies (n = 2), did not report FMD or NMD (n = 2), used another training method to carry out exercise-based CR (n = 1), and did not report/perform training prescription (n = 4). From the 21 studies included for qualitative synthesis, 18 were included for meta-analysis and three were excluded due to insufficient information to calculate the ES [45–47]. Although efforts were made to find unpublished studies, all included studies had been published in peer-reviewed journals.

Study characteristics

Study and participant characteristics are summarised in ▶ **Table 1**. The 21 included studies are from 14 countries and were published from 2002 to 2021. Twelve studies (57 %) were controlled studies, of which nine were randomised, and nine (43 %) were non-controlled studies. Two controlled studies (9.5 %) were multiple intervention studies with a shared CG. The 21 studies provided 29 pre-to post-intervention comparisons and 15 controlled comparisons, and enrolled 1,245 CAD patients (963 in the EGs and 282 in the CGs). The total sample size ranged from nine to 209 patients. The sample size in the EGs ranged from nine to 146 patients, with a mean ± *SD* age of 60.5 ± 4.3 years (min to max: 54.0 to 68.0 years), while the sample size in the CGs varied from nine to 50 patients, with a mean ± *SD* age of 60.4 ± 3.8 years (min to max: 52.9 to 66.6 years). Two studies (9.5 %) included exclusively male patients and 19 (90.5 %) recruited a mixed sample.

The intervention characteristics can be found in ▶ **Table 2**. Sixteen studies (76 %) performed exclusively an exercise-based CR programme and five (24 %) used a multicomponent CR programme including exercise training. Sixteen studies (76 %) carried out supervised exercise training sessions and five (24 %) combined supervised and home-based training sessions. Although the number of training sessions per week varied from two to 12 and the intervention length ranged from two to 24 weeks, most of the included studies performed three sessions a week (13 studies; 62 %) during an exercise-based CR programme for a duration of eight to 16 weeks (14 studies; 67 %). From the 29 pre- to post-intervention comparisons included in our systematic review, 24 (83 %) performed AT, one (3 %) carried out RT, and four (14 %) used CT. From the 28 analysis units that included AT (alone or combined with RT), 25 (89 %) performed MIT and three (11 %) used HIIT.

The endothelial and vascular smooth muscle function assessment characteristics are presented in ▶ **Table 2**. Regarding FMD, 20 studies (95 %) assessed FMD in the brachial artery and one (5 %) appraised FMD in the brachial and tibial arteries. Fourteen studies (67 %) placed the cuff distal to the assessed artery (i. e. forearm and below antecubital fossa), four (19 %) used a proximal cuff placement (i. e. upper arm), and three (14 %) did not report this information. Most of the included studies (71 %) carried out a 5-min occlusion period to induce reactive hyperaemia. The assessment of the arterial diameter after occlusion ranged from 45 to 180 s. Regarding NMD, 14 studies (93 %) assessed NMD in the brachial artery and one (7 %) in the brachial and tibial arteries. Fourteen studies (93 %) assessed NMD after sublingual administration and one (7 %) did not report the means of administration. Ten studies (67 %) administered 0.4 mg of nitroglycerin to assess endothelium-independent dilation, two (13 %) 0.3 mg, one (7 %) 0.8 mg, and two (13 %) did not report this information. The assessment of the arterial diameter after nitroglycerin administration ranged from 3 to 10 min. Four studies (19 %) used automated analysis to assess FMD and NMD [48–51], six (29 %) used manual analysis [47, 52–56] and 11 (52 %) did not report this information [45, 46, 57–65].

Risk of bias assessment

Among the 12 included randomised studies, four (33 %) had high risk of overall bias [60, 63–65] and eight (67 %) showed some concerns [48, 49, 52, 54–57, 62]. The overall risk of bias of the three non-randomised studies (100 %) was judged as critical [58, 59, 61]. Deviation from the intended intervention and confounding were the most frequent domains causing downgrading in randomised and non-randomised studies, respectively (see Supplementary Figs. 1 and 2). The risk of bias of the three single intervention studies (100 %) was rated at high risk due to lack of comparability [50, 51, 53].

Outcome measures

Flow-mediated dilation

Meta-analysed data from 18 studies (26 analysis units) showed a statistically significant improvement ($p < .001$) in FMD after an exercise-based CR programme, and the overall SMC reached a moderate effect (n = 737 patients; $SMC_+ = 1.04$ [95 % CI = 0.76 to 1.31]; ▶ **Fig. 2**). The heterogeneity test reached statistical significance ($p < .001$) and inconsistency was high ($I^2 = 92$ %). Therefore, the in-

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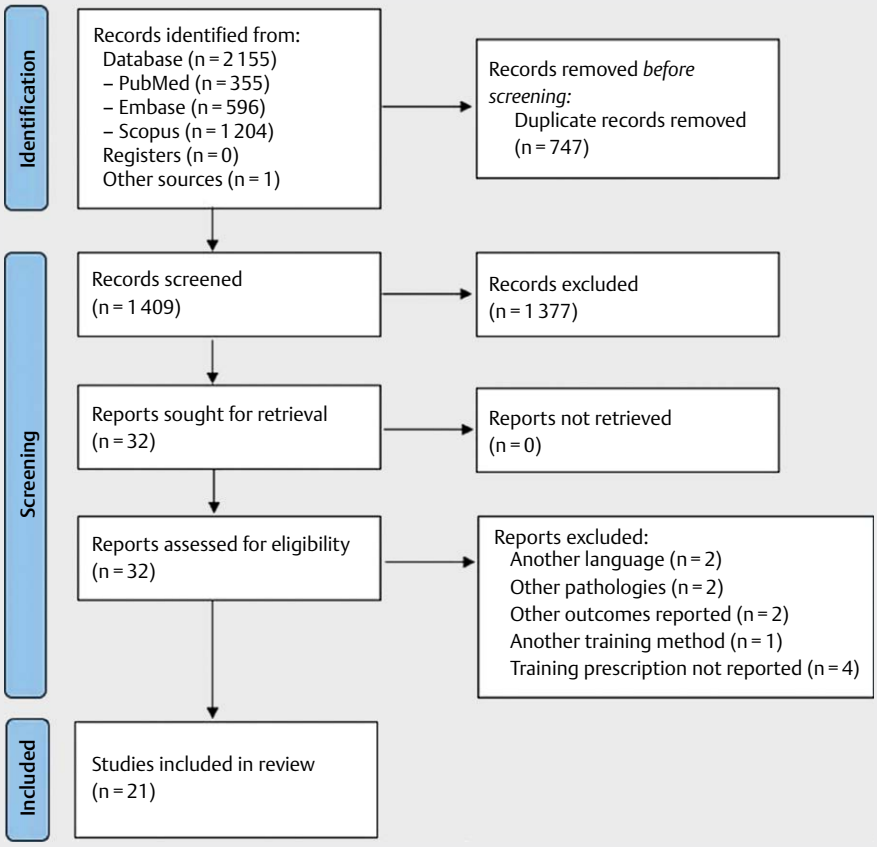

▶ **Fig. 1** Flow chart of the systematic review process.

fluence of potential moderator variables on the training-induced on FMD was analysed.

Subgroup analyses and meta-regressions for the training-induced effect on FMD can be found in ▶ **Table 3**. None of the analysed variables reached statistical significance ($p > .050$), showing no influence of any of these moderator variables on the training-induced effect on FMD. Regarding publication bias, no asymmetry was found in the funnel plot for FMD, and no ESs were imputed by the trim-and-fill method (▶ **Fig. 3**). Therefore, publication bias can be discarded as a threat against the validity of our findings regarding FMD.

Nitroglycerin-mediated dilation

Meta-analysed data from 13 studies (19 analysis units) showed no statistically significant change ($p = .216$) in NMD after exercise-based CR, and the overall SMC reached a trivial effect (n = 603 patients; $SMC_+ = 0.05$ [95 % CI = –0.03 to 0.13]; ▶ **Fig. 4**). The heterogeneity test did not reach statistical significance ($p = .162$), and inconsistency was low ($I^2 = 23$ %). Therefore, the influence of potential moderator variables on the training-induced effect on NMD was not analysed. Light asymmetry was found in the funnel plot for NMD results, and five missed ESs were imputed by the trim-and-fill method (▶ **Fig. 5**). The pooled SMC non-significantly diminished (from 0.05 [95 % CI = –0.03 to 0.13] to –0.01 [95 % CI = –0.09 to 0.08]) following imputation analysis.

Sensitivity analyses

The results did not change after deleting studies that reported statistical information as median and range or interquartile range [54, 65] for FMD (n = 658 patients; $SMC_+ = 1.06$ [95 % CI = 0.75 to 1.37]) and NMD (n = 524 patients; $SMC_+ = 0.02$ [95 % CI = –0.06 to 0.10]). Regarding the impact of including/excluding each individual analysis unit in our findings, even though the conclusions did not change for FMD, we observed a small decrease in the pooled SMC and heterogeneity magnitudes after removing one analysis unit, which performed RT [55] (n = 683 patients; $SMC_+ = 0.93$ [95 % CI = 0.72 to 1.14]; $I^2 = 85$ %).

In controlled comparisons (i. e. SMD), even though a slight increase and decrease in the magnitude of the pooled ES and heterogeneity were found for FMD, respectively (n = 611 patients; $SMD_+ = 1.16$ [95 % CI = 0.81 to 1.51]; $I^2 = 81$ %; Supplementary Fig. 3]), the conclusions were similar to those with pre- to post-intervention comparisons (i. e. SMC) (see ▶ **Fig. 2**), whereas no changes were found for NMD (n = 509 patients; $SMD_+ = 0.03$ [95 % CI = –0.15 to 0.20]; $I^2 = 23$ %; Supplementary Fig. 4) (see ▶ **Fig. 4**). Regarding non-standardised results (i. e. MD), our findings showed a statistically significant FMD increase of 3.62 % [95 % CI = 2.62 to 4.62 %],

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▶ **Table 1** Study and participants characteristics

Study (author, year)	Group; training method	Study characteristics	Participant characteristics	
		Country; study design; journal	Final sample size; mean percentage; age	Body mass index; cardiorespiratory fitness; left ventricular ejection fraction
Ades et al. [52], 2011	CR; AT (High EE)	USA; multiple intervention, randomised study; Chest	23; 74 %; 66.0 ± 9.0 years	32.2 ± 3.7 kg · m^{-2}; 22.3 ± 6.6 ml · kg^{-1} · min^{-1}; NR
	CR; AT (Low EE)		15; 87 %; 62.0 ± 9.0 years	32.5 ± 4.5 kg · m^{-2}; 21.4 ± 4.1 ml · kg^{-1} · min^{-1}; NR
Aikawa et al. [53], 2015	CR; CT	Brazil; single intervention study; Rev Bras Med Esporte	9; 56 %; 66 (min–max: 50–82) years	27.1 ± 2.8 kg · m^{-2}; NR; NR
Blumenthal et al. [45], 2012 *	CR; AT	USA; randomised controlled study; J Am Coll Cardiol	36; 67 %; 64.7 ± 11.0 years	NR; 19.5 ± 4.8 ml · kg^{-1} · min^{-1}; NR
	CG		23; 87 %; 63.5 ± 11.4 years	NR; 20.1 ± 7.4 ml · kg^{-1} · min^{-1}; NR
Blumenthal et al. [46], 2005 *	CR; AT	USA; randomised controlled study; JAMA	44; 70 %; 62.0 ± 10.5 years	29.9 ± 5.7 kg · m^{-2}; 19.1 ± 6.0 ml · kg^{-1} · min^{-1}; 59.0 ± 9.5 %
	CG		38; 84 %; 63.0 ± 9.0 years	29.8 ± 4.0 kg · m^{-2}; 20.2 ± 5.2 ml · kg^{-1} · min^{-1}; 57.0 ± 11.0 %
Cornelissen et al. [47], 2014 *	CR; AT	Belgium; single intervention study; Eur J Prev Cardiol	146; 84 %; 61.8 ± 8.8 years	27.4 ± 4.1 kg · m^{-2}; 19.1 ± 5.6 ml · kg^{-1} · min^{-1}; NR
Currie et al. [48], 2013	CR; AT (MIT)	Canada; multiple intervention, randomised study; Med Sci Sports Exerc	11; NR (mixed sample); 68.0 ± 8.0 years	27.3 ± 4.2 kg · m^{-2}; 18.7 ± 5.7 ml · kg^{-1} · min^{-1}; NR
	CR; AT (HIIT)		11 §; NR (mixed sample); 62.0 ± 11.0 years	27.9 ± 4.9 kg · m^{-2}; 19.8 ± 3.7 ml · kg^{-1} · min^{-1}; NR
Desch et al. [57], 2010	CR; AT	Germany; randomised controlled study; Diabetes Obes Metab	14; 79 %; 62.3 ± 6.2 years	29.8 ± 4.0 kg · m^{-2}; 21.7 ± 5.6 ml · kg^{-1} · min^{-1}; 63.8 ± 6.5 %
	CG		12; 67 %; 62.3 ± 6.5 years	31.3 ± 3.9 kg · m^{-2}; 19.3 ± 3.8 ml · kg^{-1} · min^{-1}; 60.9 ± 10.5 %
Edwards et al. [58], 2004	CR; AT	USA; non-randomised controlled study; Am J Cardiol	9; 100 %; 63.0 ± 9.0 years	30.0 ± 5.0 kg · m^{-2}; NR; NR
	CG		9; 100 %; 58.0 ± 8.0 years	28.0 ± 7.0 kg · m^{-2}; NR; NR
Gokce et al. [59], 2002	CR; AT	USA; non-randomised controlled study; Am J Cardiol	40 §; 77 %; 58.0 ± 10.0 years	31.0 ± 7.0 kg · m^{-2}; NR; NR
	CG		18 §; 72 %; 58.0 ± 11.0 years	29.0 ± 5.0 kg · m^{-2}; NR; NR
Kambič et al. [60], 2019	CR; CT	Slovenia; multiple intervention, randomised study; Front Physiol	12; 25 %; 64.9 ± 5.5 years	30.2 ± 4.3 kg · m^{-2}; NR; 62.8 ± 5.9 %
	CR; AT		12; 25 %; 56.2 ± 8.7 years	28.4 ± 3.3 kg · m^{-2}; NR; 66.0 ± 7.9 %
Kim et al. [61], 2014	CR; AT	Korea; non-randomised controlled study; Ann Rehabil Med	16; 87 %; 54.8 ± 9.5 years	25.5 ± 3.6 kg · m^{-2}; 28.6 ± 4.7 ml · kg^{-1} · min^{-1}; 57.2 ± 9.1 %
	CG		16; 94 %; 52.9 ± 8.5 years	25.7 ± 2.0 kg · m^{-2}; 31.5 ± 7.4 ml · kg^{-1} · min^{-1}; 56.9 ± 9.9 %
Luk et al. [62], 2012	CR; AT	China; randomised controlled study; Eur J Prev Cardiol	32; 75 %; 67.7 ± 9.0 years	24.7 ± 2.4 kg · m^{-2}; 29.8 ± 10.4 ml · kg^{-1} · min^{-1}; 59.9 ± 5.9 %
	CG		32; 75 %; 66.6 ± 7.9 years	25.1 ± 2.6 kg · m^{-2}; 27.4 ± 7.7 ml · kg^{-1} · min^{-1}; 60.4 ± 6.1 %
Munk et al. [54], 2009	CR; AT	Norway; randomised controlled study; Am Heart J	20; 85 %; 57.0 ± 14.0 years	27.1 ± 5.2 kg · m^{-2}; 23.2 ± 5.7 ml · kg^{-1} · min^{-1}; 65.0 ± 9.0 %
	CG		20; 80 %; 61.0 ± 10.0 years	27.7 ± 4.5 kg · m^{-2}; 19.1 ± 6.4 ml · kg^{-1} · min^{-1}; 65.0 ± 9.0 %
Sixt et al. [63], 2008	CR; AT	Germany; randomised controlled study; Eur J Cardiovasc Prev Rehabil	13; 77 %; 64.0 ± 6.0 years	29.2 ± 4.3 kg · m^{-2}; 21.5 ± 6.6 ml · kg^{-1} · min^{-1}; 65.0 ± 6.0 %
	CG		10; 70 %; 64.0 ± 6.0 years	31.7 ± 4.0 kg · m^{-2}; 21.1 ± 4.7 ml · kg^{-1} · min^{-1}; 62.0 ± 11.0 %
Tagashira et al. [64], 2021	CR; AT (AeT)	Japan; multiple intervention, randomised study; Heart vessels	25; 72 %; 63.4 ± 2.4 years	22.4 ± 3.1 kg · m^{-2}; 20.6 ± 1.6 ml · kg^{-1} · min^{-1}; 44.8 ± 6.3 %
	CR; AT (> AeT)		32; 69 %; 62.8 ± 2.9 years	23.6 ± 4.3 kg · m^{-2}; 21.5 ± 2.4 ml · kg^{-1} · min^{-1}; 48.8 ± 9.5 %
Van Craenenbroeck et al. [49], 2015	CR; AT (MIT)	Belgium; multiple intervention, randomised study; Am J Physiol Heart Circ Physiol	89; 89 %; 59.9 ± 9.2 years	28.5 ± 4.3 kg · m^{-2}; 22.2 ± 5.6 ml · kg^{-1} · min^{-1}; 56.8 ± 7.7 %
	CR; AT (HIIT)		85; 91 %; 57.0 ± 8.8 years	28.0 ± 4.4 kg · m^{-2}; 23.3 ± 5.8 ml · kg^{-1} · min^{-1}; 57.1 ± 8.5 %

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▶ **Table 1** Continued.

Study (author, year)	Group; training method	Study characteristics	Participant characteristics	
		Country; study design; journal	Final sample size; mean percentage; age	Body mass index; cardiorespiratory fitness; left ventricular ejection fraction
Vasić et al. [65], 2019	CR; AT (Land)	Slovenia; multiple intervention, randomised controlled study; Front Physiol	30; 70 %; 62.4 ± 7.6 years	29.0 (26.5–31.6) kg · m^{-2} &; 13.1 ± 2.8 ml · kg^{-1} · min^{-1}; NR
	CR; AT (Water)		29; 83 %; 56.7 ± 8.4 years	30.0 (27.1–32.6) kg · m^{-2} &; 14.6 ± 3.3 ml · kg^{-1} · min^{-1}; NR
	CG		30; 80 %; 60.6 ± 8.3 years	29.3 (26.8–30.9) kg · m^{-2} &; 16.6 ± 3.6 ml · kg^{-1} · min^{-1}; NR
Vona et al. [55], 2009	CR; AT	Switzerland; multiple intervention, randomised controlled study; Circulation	52; 75 %; 56.0 ± 6.0 years	26.5 ± 2.4 kg · m^{-2}; 22.0 ± 1.2 ml · kg^{-1} · min^{-1}; 57.0 ± 7.0 %
	CR; RT		54; 72 %; 57.0 ± 8.0 years	25.9 ± 2.8 kg · m^{-2}; 22.4 ± 1.2 ml · kg^{-1} · min^{-1}; 58.0 ± 9.0 %
	CR; CT		53; 75 %; 55.0 ± 9.0 years	26.3 ± 2.5 kg · m^{-2}; 21.7 ± 1.5 ml · kg^{-1} · min^{-1}; 56.0 ± 10.0 %
	CG		50; 74 %; 58.0 ± 7.0 years	25.7 ± 3.4 kg · m^{-2}; 22.3 ± 1.3 ml · kg^{-1} · min^{-1}; 59.0 ± 6.0 %
Vona et al. [56], 2004	CR; AT	Italy; randomised controlled study; Am Heart J	28; 75 %; 56.0 ± 6.0 years	26.5 ± 2.0 kg · m^{-2}; 24.9 ± 7.4 ml · kg^{-1} · min^{-1}; 55.0 ± 7.0 %
	CG		24; 79 %; 57.0 ± 8.0 years	25.7 ± 6.0 kg · m^{-2}; 24.2 ± 8.8 ml · kg^{-1} · min^{-1}; 58.0 ± 7.0 %
Walsh et al. [50], 2003	CR; CT	Australia; single intervention study; J Appl Physiol	10; 100 %; 55.0 ± 6.3 years	28.8 ± 3.8 kg · m^{-2}; 27.0 ± 5.4 ml · kg^{-1} · min^{-1}; NR
Ziegler et al. [51], 2006	CR; AT	Austria; single intervention study; Arch Phys Med Rehabil	13; 85 %; 54.0 ± 9.0 years	NR; NR; NR

AeT, aerobic threshold; AT, aerobic training; CG, non-exercise control group; CR, exercise-based cardiac rehabilitation group; CT, combined training; EE, energy expenditure; HIIT, high intensity interval training; MIT, moderate intensity training; NR, not reported; RT, resistance training; * Excluded from quantitative synthesis; $ The number of patients included in the FMD and/or NMD assessments was different; Values are reported as mean ± SD unless otherwise is stated; & median (25th to 75th percentile)

and a non-statistically significant NMD increase of 0.11 % [95 % CI = –0.81 to 1.03 %] (Supplementary Figs. 5 and 6, respectively).

Discussion

This systematic review with meta-analysis investigated the effect of exercise-based CR on endothelial and vascular smooth muscle function, assessed by FMD and NMD, respectively, in patients with CAD. Moreover, the impact of potential moderator characteristics on the training-induced effect on endothelial and vascular smooth muscle function was also studied in an attempt to explain inconsistencies in results of published empirical studies. Our findings showed that exercise-based CR improves endothelial function, assessed by FMD, in patients with CAD. Despite high inconsistency in the results of included studies, our heterogeneity analyses showed no influence of any of the analysed trial-level characteristics on the training-induced effect on FMD. We also found no change in NMD after exercise-based CR, and no inconsistency was found in the results of included studies. These findings support our hypotheses that exercise-based CR is a non-pharmacological treatment for improving endothelial function in CAD patients, whereas its effect on vascular smooth muscle function is more limited. Contrary to our hypothesis, the effect of exercise-based CR on endothelial function in patients with CAD is not affected by study or training characteristics.

Flow-mediated dilation

Our finding that exercise-based CR improves FMD in patients with CAD is in line with results of previous systematic reviews and meta-analyses that included studies investigating patients affected by other pathologies [20–22, 66, 67]. Several mechanisms have been proposed to explain the effect of exercise training on endothelial function. First, exercise training increases shear stress, which increases NO bioavailability and decreases production of pro-inflammatory biomarkers (i. e. C-reactive protein and cytokines). Moreover, exercise training induces mobilisation of bone-marrow derived EPCs, which also promote endothelial repair [23–25, 68, 69]. We found that the magnitude of the effect of exercise-based CR in CAD patients (SMC_+ = 1.04 [95 % CI = 0.76 to 1.31]) is the same magnitude of the effect previously reported in CHF patients (SMD_+ = 1.08 [95 % CI = 0.70 to 1.46]) [20], even though authors estimated the effect of exercise training compared with non-exercise controls (i. e. SMD). Moreover, our sensitivity analyses demonstrated the same results when only controlled studies were included, supporting the validity of our findings. These results also support that usual care is suboptimal for enhancing endothelial-dependent dilation. We also note that Qiu et al. [21], who used the MD as the ES index, reported that exercise training enhanced FMD by 1.77 % (95 % CI = 0.94 to 2.59 %) in type 2 diabetes patients, whereas our sensitivity analyses showed that exercise-based CR increased FMD by 3.62 % (95 % CI = 2.62 to 4.62 %) in CAD patients. The lower train-

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▶ **Table 2** Intervention and assessment characteristics.

Study (author)	Group; training method	Intervention characteristics		FMD assessment characteristics	NMD assessment characteristics
		Setting; lifestyle program; aerobic training intensity; length	Sessions a week; session length; volume; intensity	Artery; cuff placement; occlusion length; occlusion pressure; post-occlusion assessment length	Artery; via administration; dose; post-administration assessment length
Ades et al. [52]	CR; AT (High EE)	Supervised and home-based sessions; multicomponent; MIT; 16 weeks	1–3 s/w (supervised) + 2 – 4 s/w (home); 45– 60 min; 25 min + 2 × 8 min; NR (supervised)	Brachial; proximal (upper arm); 300 s; 50 mmHg above SBP; 60 s [$]	Brachial; sublingual administration; 0.4 mg nitroglycerin; 180 s [$]
	CR; AT (Low EE)		1–3 supervised; 25–40 min; 25 min + 2 × 8 min; NR		
Aikawa et al. [53]	CR; CT	Supervised; exercise only; MIT; 24 weeks	3 s/w; 50 min; AT: 2 × 15 min; 30–60 % HR max RT: 6 sets x 10 reps (lower and upper); 30–60 % 1RM	Brachial; NR; 300 s; 50 mmHg above SBP; 60 s [$]	Brachial; sublingual administration; 0.4 mg nitroglycerin; NR
Blumenthal et al. [45] *	CR; AT	Supervised; exercise only; MIT; 16 weeks	3 s/w; 30 min; 30 min; 70–85 % HR reserve	Brachial; distal (forearm); 300 s; about 200 mmHg; 10-120 s	–
	CG	–	–		
Blumenthal et al. [46] *	CR; AT	Supervised; exercise only; MIT; 16 weeks	3 s/w; 35 min; 35 min; 70–85 % HR reserve	Brachial; distal (forearm); 300 s; about 200 mmHg; 10-120 s	Brachial; sublingual administration; 0.4 mg nitroglycerin; 180-300 s
	CG	–	–		
Cornelissen et al. [47] *	CR; AT	Supervised; exercise only; MIT; 12 weeks	3 s/w; 90 min (total length); NR; 60–90 % HR reserve	Brachial; distal (forearm); 300 s; 200 mmHg or 50 mmHg above SBP; 0–180 s	–
Currie et al. [48]	CR; AT (MIT)	Supervised; exercise only; MIT or HIIT (based on the allocated group); 12 weeks	2 s/w; 30–50 min; 30–50 min; 58 % PPO	Brachial; distal (forearm); 300 s; 200 mmHg; 0–180 s	Brachial; sublingual administration; 0.4 mg nitroglycerin; 0–600 s
	CR; AT (HIIT)		2 s/w; 20 min; 10 × 1 min (work)/1 min (active rest); 89 %, 102 %, and 110 % PPO (work)/10 % PPO (active rest)		
Desch et al. [57]	CR; AT	Supervised and home-based sessions; exercise only; MIT; 24 weeks	Daily at home + 2 s/w supervised; 30 min (home), 90 min (total length) (supervised); 30 min (home), 90 min (supervised); 75 % HR max	Brachial; NR; NR; NR; 60 s [$]	Brachial; NR; NR; NR
	CG	–	–		
Edwards et al. [58]	CR; AT	Supervised; exercise only; MIT; 12 weeks	3 s/w; 15–50 min; 15–50 min; 40–85 % HR reserve	Brachial; proximal (upper arm); 300 s; NR; 60 s [$]	–
	CG	–	–		
Gokce et al. [59]	CR; AT	Supervised; exercise only; MIT; 10 weeks	3 s/w; 30–40 min; 30–40 min; 40–85 % HR reserve	Brachial and tibial; proximal (upper arm) and proximal (mid-calf region); 300 s; above 200 mmHg; 60 s [$]	Brachial and tibial; sublingual administration; 0.4 mg; 180 s [$]
	CG	–	–		
Kambič et al. [60]	CR; CT	Supervised; multicomponent; MIT; 8 weeks	AT: 3 s/w (see AT group) + RT with blood flow restriction: 2 s/w; leg extension x 3 sets x 8–12 reps/45 s (rest); 30–40 % 1RM	Brachial; distal (forearm); 270 s; 50 mmHg above SBP; 60 s [$]	–
	CR; AT		3 s/w; 45 min; 45 min; 70–80 % HR max		

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▶ **Table 2** Continued.

Study (author)	Group; training method	Intervention characteristics		FMD assessment characteristics	NMD assessment characteristics
		Setting; lifestyle program; aerobic training intensity; length	**Sessions a week; session length; volume; intensity**	**Artery; cuff placement; occlusion length; occlusion pressure; post-occlusion assessment length**	**Artery; via administration; dose; post-administration assessment length**
Kim et al. [61]	CR; AT	Supervised; exercise only; MIT; 6 weeks	3 s/w; 30 min; 3 ×8 min; 40–85 % HR reserve	Brachial; distal (forearm); 300 s; 200 mmHg or 50 mmHg above SBP; 45, 60, and 120 s [$]	–
	CG	–	–		
Luk et al. [62]	CR; AT	Supervised; multicomponent; MIT; 8 weeks	3 s/w; 50 min; 50 min; gradually increased until 80 % HR max	Brachial; distal (forearm); 300 s; 250 mmHg; 60 s [$]	Brachial; sublingual administration; 0.4 mg nitroglycerin; 300 s [$]
	CG	–	–		
Munk et al. [54]	CR; AT	Supervised; exercise only; HIIT; 24 weeks	3 s/w; 30 min; 4 ×4 min (work)/3 min (active rest); 80–90 % HR max (work)/60–70 % HR max (active rest)	Brachial; NR; 300 s [#]; 50 mmHg above SBP [#]; 45–60 s [#]	Brachial; sublingual administration [#]; 0.4 mg [#]; 180–240 s [#]
	CG	–	–		
Sixt et al. [63]	CR; AT	Supervised and home-based sessions; exercise only; MIT; 4 weeks	NR; 90 min (supervised), 30 min (home); 6 ×15 min (supervised), 30 min (home) + 1 hour (supervised); 70 % HR max	Brachial; distal (forearm); 300 s; 50 mmHg above SBP; 0–120 s	Brachial; sublingual administration; 0.4 mg nitroglycerin; 0–120 s
	CG	–	–		
Tagashira et al. [64]	CR; AT (AeT)	Supervised and home-based sessions; multicomponent; MIT; 16 weeks	3 s/w; 30 min; 30 min; intensity at AeT HR (AeT group) or intensity at 105 % AeT HR (> AeT group)	Brachial; distal (forearm); 300 s; 50 mmHg above SBP; NR	–
	CR; AT (> AeT)				
Van Craenenbroeck et al. [49]	CR; AT (MIT)	Supervised; exercise only; MIT or HIIT (based on the allocated group); 12 weeks	3 s/w; 37 min; 37 min; 70–75 % HR peak	Brachial; distal (forearm); 300 s; 200 mmHg or 60 mmHg above SBP; 0–180 s	Brachial; sublingual administration; 0.4 mg nitroglycerin; 180–540 s
	CR; AT (HIIT)		3 s/w; 38 min; 4 ×4 min (work)/3 min (active rest); 90–95 % HR peak (work)/50–70 % HR peak (active rest)		
Vasić et al. [65]	CR; AT (Land)	Supervised; multicomponent; MIT; 2 weeks	12 s/w (twice daily); 20; 2 ×20 min; 60–80 % HR peak	Brachial; distal (forearm); 270 s; 50 mmHg above SBP; 60–90 s	Brachial; sublingual administration; 0.4 mg nitroglycerin; 180–240 s
	CR; AT (Water)				
	CG	–	–		
Vona et al. [55]	CR; AT	Supervised; exercise only; MIT (if applicable); 4 weeks	4 s/w; 40 min; 40 min; 75 % HR peak	Brachial; distal (forearm); 300 s; 260 mmHg; 0–90 s	Brachial; sublingual administration; 0.3 mg nitroglycerin; 300 s [$]
	CR; RT		4 s/w; NR; 4 sets x 10 exercises x 10–12 reps; 60 % 1RM		
	CR; CT		2 s/w AT (see AT group) + 2 s/w RT (see RT group)		
	CG	–	–		

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▶ **Table 2** Continued.

Study (author)	Group; training method	Intervention characteristics		FMD assessment characteristics	NMD assessment characteristics
		Setting; lifestyle program; aerobic training intensity; length	**Sessions a week; session length; volume; intensity**	**Artery; cuff placement; occlusion length; occlusion pressure; post-occlusion assessment length**	**Artery; via administration; dose; post-administration assessment length**
Vona et al. [56]	CR; AT	Supervised; exercise only; MIT; 12 weeks	3 s/w; 40 min; 40 min; 75 % HR peak	Brachial; distal (forearm); 300 s; 260 mmHg; 0–90 s	Brachial; sublingual administration; 0.3 mg nitroglycerin; 300 s [$]
	CG	–-	–		
Walsh et al. [50]	CR; CT	Supervised and home-based sessions; exercise only; MIT; 8 weeks	2 s/w (supervised) 1 s/w (home); NR; 1–3 circuits x 16 stations (8 resistance exercise + 8 cycle stations, alternated) x 15 reps or 45 s (work)/15 s (rest); 55–65 % 1RM or 70–85 % HR peak (supervised)/45–60 min; 70–85 % HR peak (home)	Brachial; distal (forearm); 300 s; 200 mmHg; 0–120 s	Brachial; sublingual administration; 0.4 mg nitroglycerin; 0–300 s
Ziegler et al. [51]	CR; AT	Supervised; exercise only; MIT; 8 weeks	2 s/w; 20 min; 20 min; 50 % maximal functional capacity	Brachial; proximal (upper arm); 270 s; 250 mmHg; 0–180 s	Brachial; sublingual administration nitroglycerin; 0.8 mg; 0–240 s

*1*RM, one-repetition maximum; AeT, aerobic threshold; AT, aerobic training; CG, non-exercise control group; CR, exercise-based cardiac rehabilitation group; CT, combined training; EE, energy expenditure; FMD, flow-mediated dilation; HIIT, high intensity interval training; HR, heart rate; MIT, moderate intensity training; NA, not applicable; NMD, nitroglycerin-mediated dilation; NR, not reported; PPO, peak power output; RT, resistance training; SBP, systolic blood pressure; s/w, sessions a week; * Excluded from quantitative synthesis; [$]Punctual measurement/s was/were performed in this/these moment/s; [#] Information according to guidelines; Session length was reported without warm-up and cool-down unless otherwise is stated

ing-induced effect on FMD found in type 2 diabetes patients, compared to cardiac patients, may be explained by the diminished ability of the endothelium to produce NO after exercise training because of the persistent hyperglycaemia found in diabetic patients [70, 71]. Moreover, the potential of exercise training to mobilise EPCs from bone marrow to circulation also seems to be lower in these patients [72]. Taken together, these findings show that exercise training is a non-pharmacological treatment for improving endothelial dysfunction in patients. The enhancement of FMD after exercise-based CR is of clinical importance since there is evidence that shows that every 1 % increase in FMD was correlated with an 8 to 13 % lower risk of cardiovascular events [12, 73, 74].

It should be noted that our findings are based mainly on studies that used AT as the training method (24 analysis units), whereas only four and one analysis units carried out CT and RT, respectively. Although our heterogeneity analyses showed no differences in FMD improvements based on the training method used (i. e. AT vs. CT), the low number of studies that carried out RT, alone or combined with AT, is very low, limiting the scope of this finding. Similarly, Pedralli et al. [75] found that different training methods similarly enhance FMD in patients with prehypertension or hypertension, a major risk factor for CAD. Contrastingly, Lee et al. [67] reported that the effect of AT is statistically higher than the effect of CT or RT alone in type 2 diabetes patients. Additionally, Qiu et al. [21] found that the effect of CT on FMD (MD_+ = 2.49 % [95 % CI = 1.17 to 3.81 %]) was higher than the effect of AT (MD_+ = 1.21 % [95 % CI = 0.23 to 2.19 %]) in type 2 diabetes patients, whereas the effect of RT only showed a trend (MD_+ = 1.60 % [95 % CI = –0.52 to 3.72 %]). Nevertheless, only one study that performed RT was also included in this systematic review. Moreover, although statistical comparisons based on the training method were not performed, CIs were overlapping, showing no statistical difference between the estimated ESs. Taken together, these findings seem to support that the inclusion of RT in exercise-based CR programmes does not increase the positive effects of AT alone on FMD, even though the number of studies which appropriately studied the effect of CT on FMD in patients with CAD is low. Therefore, future studies should compare the effects of CT versus AT on FMD to confirm our findings. Although the effect of RT alone has not been well studied, evidence shows that AT is suitable for improving endothelial function and, therefore, should be applied in exercise-based CR programmes with or without RT.

Our subgroup analyses showed no influence of AT intensity (i. e. MIT vs. HIIT) on the training-induced effect on FMD. Similarly, Qiu et al. [21] found no differences based on the AT intensity for improving FMD in type 2 diabetes patients. Interestingly, Lee et al. [67] reported that higher FMD enhancement was attained after lower AT intensity-based CR programmes. Conversely, previous meta-analyses showed that HIIT is more effective than MIT for improving CRF in cardiac patients [76, 77], and improved FMD has been shown to be associated with improved CRF [78]. Nevertheless, enhancement of the CRF is also affected by other underlying mechanisms [79], which could explain the lack of influence of intensity on the training-induced effect on FMD. Regarding volume variables, our heterogeneity analyses also showed no influence of the number of training sessions performed a week and the intervention length on the training-induced effect on FMD. Nonetheless, most of the included studies performed three sessions a week

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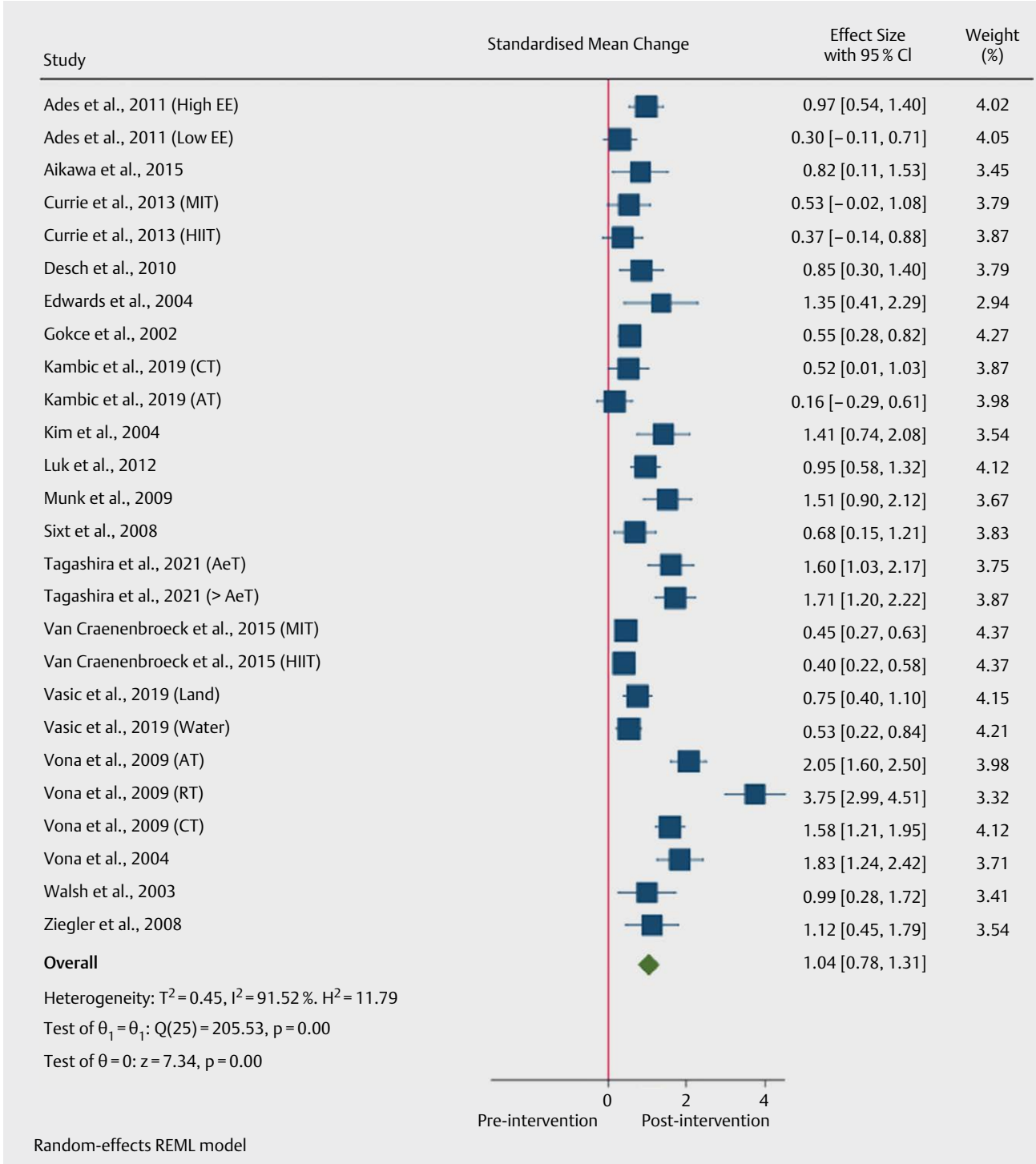

▶ **Fig. 2** Forest plot of standardised mean change indices for flow-mediated dilation .

for between eight and 16 weeks. Previous studies have highlighted the critical role of manipulating training variables (e. g. frequency, intensity, and duration) to facilitate long-term adaptations [80]. Thus, we hypothesise that the lack of influence of these variables could be due to incorrect management of these training variables. In sum, it seems that aerobic MIT performed three days a week during eight to 16 weeks is a sufficient stimulus for improving FMD in CAD patients, and increased training load (i. e. training method [CT], intensity, and volume) should be used for increasing the stimulus and obtaining long-term effects.

Other heterogeneity sources should be considered to explain the inconsistency found in our findings. Previous studies have reported that training adaptations could be related to participant characteristics (e. g. CRF, wait time to start exercise-based CR, par-

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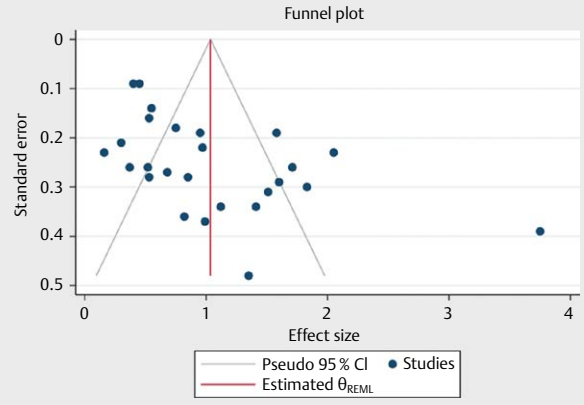
▶ **Table 3** Moderator variables analysis for the training-induced effect on flow-mediated dilation.

Categorical variables				**Test for subgroup differences**	
Moderator	**Category**	**K**	**SMC (95 % CI)**	***Chi*²**	***p*[a]**
Patients' allocation	Randomised	20	1.05 (0.70–1.40)	0.17	.681
	Non-randomised	6	0.95 (0.61–1.28)		
Setting	Supervised	20	1.01 (0.66–1.36)	0.23	.628
	Mixed	6	1.14 (0.79–1.48)		
Lifestyle programme	Exercise only	16	1.16 (0.78–1.55)	1.77	.183
	Multicomponent	8	0.82 (0.48–1.15)		
Training method *	Aerobic training	21	0.92 (0.68–1.16)	0.10	.756
	Combined training	4	1.01 (0.50–1.52)		
Aerobic training intensity	MIT	22	0.96 (0.73–1.19)	0.41	.523
	HIIT	3	0.72 (0.03–1.42)		
Continuous variables				**Test of residual heterogeneity**	
Moderator	**K**	***B* (95 % CI)**	***p***	***Chi*²**	***p*[a]**
Publication year	26	−0.030 (−0.080–0.020)	.238	193.33	< .001
Sample size	26	0.005 (−0.008–0.018)	.439	191.39	< .001
Mean percentage	24	0.006 (−0.011–0.022)	.512	199.85	< .001
Intervention length, weeks	26	−0.013 (−0.058–0.032)	.577	201.97	< .001
Training frequency, s/w	22	−0.031 (−0.151–0.089)	.614	199.54	< .001
Total number of sessions (x10)	22	−0.004 (−0.025–0.017)	.724	194.68	< .001

B, B regression coefficient; Chi², chi-square statistic; CI, confidence interval; HIIT, high intensity interval training; I², heterogeneity index; K, number of included analysis units; MIT, moderate intensity training; p, probability associated to Z statistic for B regression coefficient; p[a], probability level associated to chi-squared statistic; s/w, sessions per week; SMC, standardised mean change; * Resistance training analysis unit was excluded from the subgroup analysis



▶ **Fig. 3** Funnel plot with trim-and-fill method for flow-mediated dilation .

ticipant age, and baseline arterial diameter) [76, 81–83]. Nevertheless, the influence of individual-level characteristics on the effect of exercise-based CR on FMD was not studied because we used aggregated information at the trial level, and spurious associations between participant characteristics and treatment effect could be found [84]. Therefore, the influence of these characteristics on the training-induced effect on endothelial-dependent dilation requires future study. Moreover, our risk of bias analysis showed that the results of included studies may be affected by systematic bias (i. e. selection bias). Future randomised studies should appropriately report random sequence generation and carry out allocation concealment to facilitate the interpretation of their findings and avoid selection bias. On the other hand, although there is consensus on how to carry out FMD assessments, methodological issues such as the use of manual analysis and cuff position used from the imaged artery for assessing endothelial dilation may affect the reproducibility of FMD [16, 85–88]. In this regard, evidence indicates that manual analyses could overestimate the effect of exercise training on FMD and increase measurement error [7]. Our systematic review showed that six studies used manual analysis and 11 did not report this information, which could explain, at least in part, the heterogeneity found in our findings without influence of any of the analysed variables on the effect of exercise-based CR on FMD. Therefore, future studies should use automated analysis to properly estimate the effect of exercise-based CR on FMD. Finally, even though included studies used different cuff positions from the imaged artery (i. e. distal and proximal), previous meta-analyses failed to find differences in the predictive ability of FMD based on the cuff position [89, 90].

Nitroglycerin-mediated dilation

We found that exercise-based CR did not enhance endothelial-independent dilation, assessed by NMD, in patients with CAD. This is in line with the results of previous meta-analyses which included studies performed in patients with CHF [20] or type 2 diabetes [22]. These findings show that exercise training does not enhance arterial smooth muscle function in patients. Nevertheless, it should be

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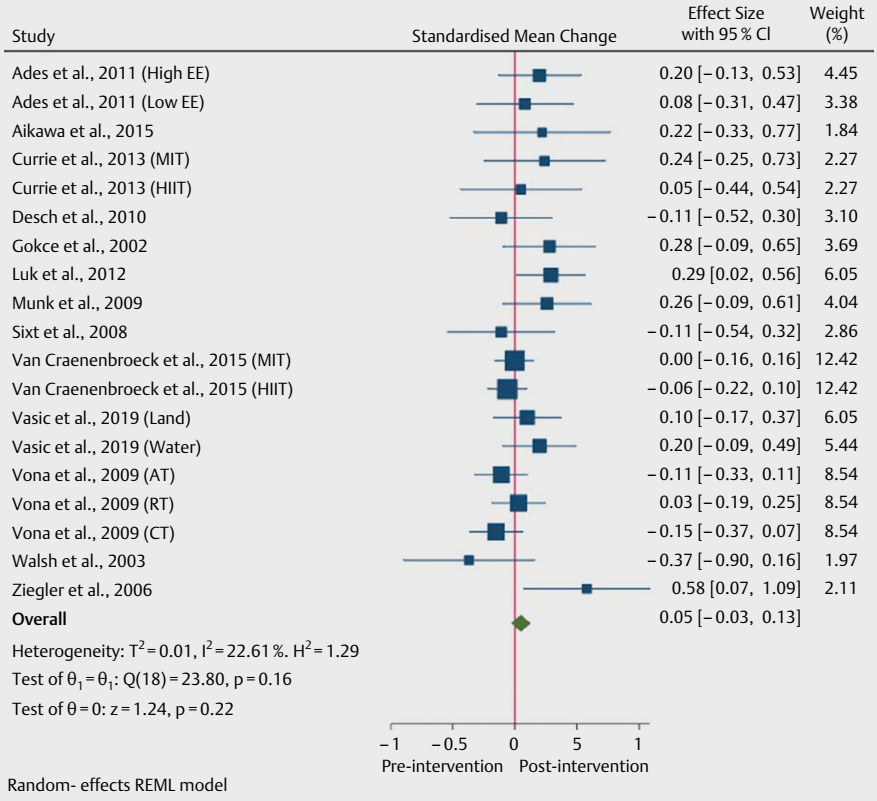
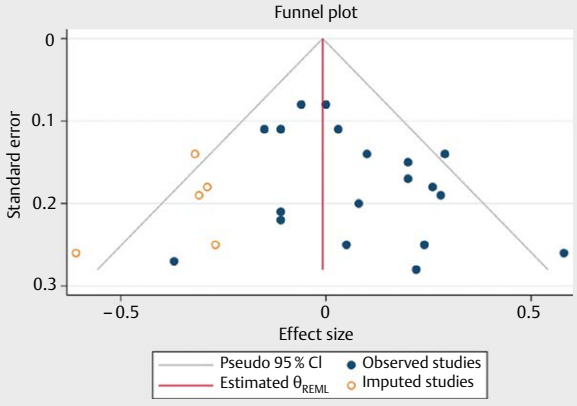


▶ **Fig. 4** Forest plot of standardised mean change indices for nitroglycerin-mediated dilation.



▶ **Fig. 5** Funnel plot with trim-and-fill method for nitroglycerin-mediated dilation.

noted that endothelial-independent dilation is normally assessed in conjunction with endothelial-dependent dilation to discard the lack of responsiveness of vascular smooth muscle cells on any observed change in FMD. Therefore, preserved endothelial-independent dilation at pre-intervention could explain the lack of effect of exercise-based CR on NMD in patients with CAD.

Strengths and limitations

This is the first systematic review with meta-analysis that has investigated the training-induced effect on endothelial and vascular smooth muscle function, assessed by FMD and NMD, respectively, in patients with CAD. Training characteristics (i. e. training method and AT intensity) were carefully coded to appropriately study their influence on the training-induced effect on FMD. Moreover, we carried out several sensitivity analyses for supporting the robustness of our decisions and for comparing our results with those obtained from meta-analyses that used other ES indices. Nonetheless, there are also some limitations that should be noted. The number of included studies that carried out RT, alone or combined with AT, is low, which limits our conclusion as to the effect of AT alone on FMD in CAD patients. Moreover, our main findings are based on within-group comparisons, which enabled a higher number of analysis units to carry out heterogeneity analyses but diminishes the internal validity of our findings.

Conclusions

Our findings showed that exercise-based CR is a non-pharmacological treatment for improving endothelial-dependent dilation in patients with CAD. We also found that exercise-based CR seems ineffective for augmenting endothelial-independent dilation in these patients. Based on our findings, we suggest that progressive exercise-based CR programmes aimed at improving endothelial-

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dependent dilation should include three aerobic MIT sessions a week for eight to 16 weeks. However, chronic exercise beyond 16 weeks may be needed for long-term maintenance of training-induced effects. Future studies should be performed to determine the influence of including RT, mainly combined with AT, on exercise-based CR programmes. Moreover, future studies should analyse the effect of AT intensity, training frequency, and intervention length on the effect of exercise-based CR on endothelial function.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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