Review Article

Coronary vasomotion and exercise-induced adaptations in coronary artery disease patients: A systematic review and meta-analysis

Azra Ahmadi[1], Valiollah Dabidi Roshan[1], Arash Jalali[2]

[1]Department of Sport Physiology, College of Physical Education and Sport Sciences, University of Mazandaran, Babolsar, Iran, [2]Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran

Background: Exercise can improve coronary blood flow in a healthy heart, but the vascular response of patients with coronary artery disease (CAD) is different. The aim of this study was to systematically review the chronic effects of exercise on coronary arterial function in CAD patients. **Materials and Methods:** Six electronic databases (PubMed, ScienceDirect, "Scopus," Web of Science, EMBASE, and Google Scholar) covering publications from 1986 to 2019 were systematically searched with related keywords. Studies were included if they investigated changes in blood flow and coronary artery diameter in response to chronic exercise training in patients with CAD. A total of 5421 studies were assessed for quality and outcomes, and finally five studies met criteria for inclusion. For metaanalysis, the results of the studies were pooled using the randomeffects model. The heterogeneity between the studies was checked using I^2 index. **Results:** The total sample population consisted of 108 CAD patients. According to the findings of this study, coronary artery function in adaptation with exercise showed that a period of exercise leads to statistically significant improvement in coronary flow velocity reserve (z = 3.15, P = 0.002; standardized mean difference [SMD] =2.33, 95% confidence interval [CI]: 0.88–3.78) (containing six trials). In addition, vasodilatory response of coronary arteries in response to endothelium-independent vasodilator nitroglycerin was investigated in three studies (containing four trials). A meta-analysis showed that performing chronic aerobic exercises did not make a significant change in the endothelium-independent vasodilator (z = 0.83, P = 0.40; SMD = −0.36, 95% CI: −1.21–0.49). **Conclusion:** Based on the results of the present study, aerobic exercises improve the endothelial function of coronary arteries and thereby the vascular vasomotion function, while the results of this meta-analysis showed no change in arterial smooth muscle's function by chronic aerobic exercises. This study reflects the lack of high- and medium-quality reports about the chronic effects of anaerobic and resistance exercises and the various methods of aerobic exercise on cardiovascular function.

Key words: Coronary artery disease, coronary, exercise, vasomotion

How to cite this article: Ahmadi A, Dabidi Roshan V, Jalali A. Coronary vasomotion and exercise-induced adaptations in coronary artery disease patients: A systematic review and meta-analysis. J Res Med Sci 2020;25:76.

INTRODUCTION

Cardiovascular diseases is a major cause of mortality in developed and developing societies.[1] Coronary artery disease (CAD) is the most common cardiovascular disease, and atherosclerosis is the main cause of CAD, but other factors can also cause CAD.[2] Epidemiological studies have shown some risk factors associated with coronary atherosclerosis, including hypercholesterolemia, smoke, hypertension, diabetes, age, male gender, family history of coronary disease, obesity, and sedentary lifestyle.[2,3] Physical activity, among all these factors, is of great importance to the prevention and treatment of CAD.[3]

Exercise training is the core of cardiac rehabilitation, with many beneficial effects for patients with CAD.[3] There is no doubt that exercise can have a direct effect on myocardial function. Exercise can improve cardiac

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_580_18

Address for correspondence: Prof. Valiollah Dabidi Roshan, Department of Sport Physiology, College of Physical Education and Sport Sciences, University of Mazandaran, Pasdaran Street, P.O. Box: 416, Mazandaran, 47415 Babolsar, Iran. E-mail: v.dabidi@umz.ac.ir, vdabidiroshan@yahoo.com

Submitted: 15-Nov-2018; **Revised:** 05-Jan-2020; **Accepted:** 21-Apr-2020; **Published:** 24-Aug-2020

contractile function, increase end-diastolic volume, cause resting bradycardia, and increase antioxidant capacity.[4] Exercise is the most important physiological stimulus for increased oxygen consumption by the heart.[5-7] Considering that heart does not have a considerable ability to increase oxygen uptake, the increased demand should be achieved by increasing coronary blood flow (CBF), so coronary arteries play a major role in oxygen delivery to the myocardium.[8]

Some studies have demonstrated that increase in CBF during exercise leads to dilation of normal blood vessels.[9] Although regulation of CBF during exercise in patients with CAD would be different, the mechanisms that regulate blood flow during exercise have not been yet clearly well determined.[5,6,10] So far, various findings have been reported on the effect of exercise on cardiovascular health. Some evidence also indicates that the type of exercise can be an important determinant in the function of healthy and diseased arteries.[11-13]

Given that measuring the function of coronary arteries is a useful tool in cardiovascular research, it can be considered as a "barometer" for the care of patients and evaluation of new therapeutic strategies.[14,15] Several invasive and noninvasive methods have been used by researchers to measure this indicator. After extensive scrutiny of literatures for conducting the present systematic review, changes in blood flow and coronary artery diameter were selected as the most common method for measuring coronary function. Despite various methods for measuring these factors, changes in blood flow are usually assessed by the indicators of coronary blood flow velocity (CBV), coronary blood flow velocity reserve (CFVR), or CBF using angiography techniques, echocardiography, magnetic resonance imaging (MRI), and positron emission tomography.[16-19] It should be noted that CFVR is an indicator, measuring the capacity of coronary circulation in relation to the maximal hyperemic blood flow, and is calculated as a ratio of hyperemic flow velocity to resting flow velocity.[20] CBF is also one of the most important indicators for the evaluation of coronary artery function. CBF is usually calculated in numerous ways in human studies and in all of them, it is dependent on vessel diameter and flow velocity[9,21] (e.g. in the evaluation by MRI, it is calculated as follows: the cross-sectional area × peak flow velocity × 0.3).

On the other hand, coronary vasomotion also is considered as one indicator of coronary artery function using various measuring techniques at the time of physiological hyperemic (e.g. during exercise) or the presence of vasodilators.[18,22,23] Due to discrepancy in evaluating the function of the coronary arteries, this study attempted to investigate all the articles that evaluated this indicator based on defined methods and using various tools and include them in systematic review.

MATERIALS AND METHODS

This systematic review was done based on Cochrane guideline and reported in accordance with the PRISMA format.[24,25] This review aimed to examine the chronic effect of exercise on the coronary artery function. Accordingly, all related articles indexed in scientific databases were collected and evaluated scientifically.

Search strategy

To avoid bias, the search was performed independently by two researchers (AA [PhD student of sport physiology] and VD [professor of sport physiology]). A librarian (PhD student in Library and Information Sciences) also advised researchers to perform the search process correctly. Duplicates were excluded, at the end of the search phase. The electronic databases – PubMed, Science Direct, Scopus, Web of Science, EMBASE, and Google Scholar – were searched for articles in English from 1986 to 2019. The search was done utilizing keywords related to coronary function (coronary vasomotion, coronary function, coronary blood flow, coronary vasodilation, coronary flow reserve, coronary diameter, coronary endothelial function, and coronary flow velocity reserve) and exercise (exercise, sport, chronic exercise, physical activity, training, endurance, aerobic exercise, anaerobic exercise, strength, running, resistance, and swim). In addition, through investigating the reference lists of the relevant studies, we tried to include more qualified studies. For example, in PubMed website, we used advanced search and inserted two keywords "coronary function" and "exercise" together with the operator "and" between two concepts to retrieve results that include all the search terms. The citations of all articles were collected in Endnote (Thomson Reuters, Philadelphia, PA, USA). However, there were many duplicate articles. Duplicate articles were removed using the software, and a more detailed search was performed on the remaining articles. First, article titles and abstracts were reviewed, and the articles were categorized with the relevant titles in a folder. After these initial reviews, the articles that had initial conditions were reviewed through their full text.

Selection of studies

The eligible studies were included according to the following criteria: (1) randomized controlled trials (RCTs) on people with CAD who received exercise training alone or combined with usual care; (2) studies that evaluated each of the following indicators: CBF, CBV, CFVR, or coronary vasomotion in adaptation to exercise training; (3) adult humans aged >18 years; and (4) duration of intervention ≥4 weeks of exercise.

Conference proceedings with an abstract alone, case reports, review articles, animal studies, studies with no detailed information, and studies among patients with other diseases such as hypertension, diabetes, heart failure, and obesity were excluded.

Data extraction and quality assessment

As mentioned earlier, choosing eligible studies and data extraction was done by two independent reviewers (AA [PhD student of sport physiology] and VD [professor of sport physiology]). Disagreements were resolved by discussion.

Based on previous studies, a standard form of data extraction was used. This checklist included the author's name, article title, year of publication, location of the study, sample size, population, and gender. Study design, quality, sample size, participants' characteristics, characteristics of exercise intervention (type, duration, and frequency of sessions and intensity and duration of intervention), and outcomes (CFV, CFVR, CBF, and coronary vasomotion) were also extracted on the basis of a form designed for this purpose.

For articles that did not include the required data in the article, if it was eligible for inclusion, an attempt was done by sending an email to the authors. If the response was not received, the article was excluded from the review process.

The quality and validity of all the included studies were evaluated using the Downs and Black Checklist for randomized and nonrandomized studies. Questions were categorized into the following five sections: reporting (10 items), external validity (3 items), internal validity (7 items), confounding and selection bias (6 items), and power (1 item). Answers were scored 0 or 1, except for one item in the reporting subscale, which scored 0–2 and the power item, which was scored 0–5. The total maximum score was therefore 31. The test–retest reliability of the Quality Index was high ($r = 0.88$).[26,27] Articles with scores between 20 and 25 were considered as the studies with average quality and scores above than 25 were rated as high-quality studies.

As blinding participants to an exercise intervention is impossible, we considered this matter in related items.

Statistical analysis

All data analyses were performed by STATA 12 (StataCorp. 2011. College Station, TX, USA) (by AJ). First, mean change and standard deviation in baseline and posttest for both exercise and control groups were extracted. As the variables were continuous, the mean difference was calculated by net changes (i.e. exercise group minus control group), and standardized mean difference (SMD) and 95% confidence interval [CI] were reported for all studies. Metan command (random-effects model) in Stata was used to analyze the data. In addition, Chi-squared and I^2 indicators were used to detect the heterogeneity among the results.

Subgroup analyses were also used for deeper investigation; in this way, the role of different factors in the results and heterogeneity was investigated.

Meta-regression was used to examine the association between the effect of exercise on CFVR and endothelium-independent vasodilator with sample size, year of publication, and quality score. Furthermore, publication bias was assessed by funnel plots and Begg's test.

RESULTS

After comprehensive review of the collected articles and references of related review articles, a total of five articles were entered into the study, which are shown in a flow diagram [Figure 1].

No study with RCT method was conducted in which the CBF was measured. The total sample size in studies that included in the systematic review was 108 people including 101 men and 7 women[Tables 1 and 2].

Participants in the three studies were all men, and there was no study in which only women comprised the sample size. In all studies, the effect of aerobic exercises was investigated. The intensity of the exercise in the articles was between 60% and 80% of VO_2 peak, and the training period varied between 4 and 14 weeks. It should be noted that two studies by Beck *et al*.[16] and Hambrecht *et al*.[22] also in terms of quality were eligible to enter the systematic review, but given that the measurements had been performed in the left internal mammary artery, they were excluded from the study.

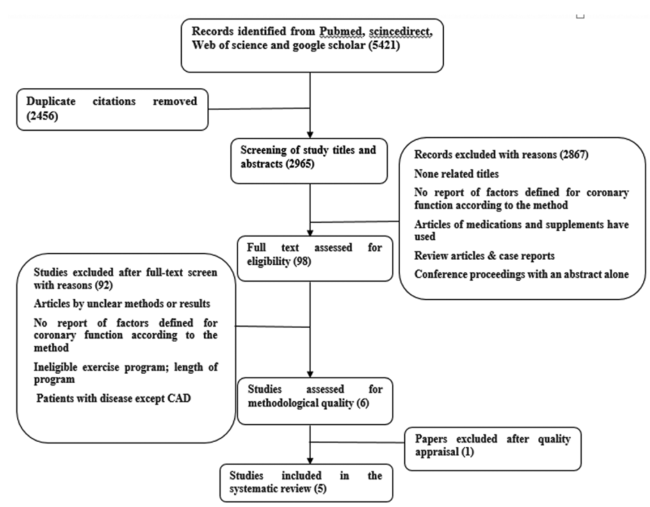

Figure 1: Flow diagram of the search and study inclusion process

Table 1: Characteristics of studies included in the systematic review and meta-analysis

Studies	Participants	Sample size	Sex	Age (years)	Exercise training program	Duration (weeks)	Measurement	Outcome measures	Outcome
Hambrecht *et al.*, 2000[29]	CAD	T: 10	Male	60±2	Exercise under close supervision six times per day for 10 min on a bicycle ergometer at 80% of the heart rate reached at peak oxygen uptake (7 days per week)	4	Angiography	Luminal diameter (Ach and NTG)	↓Vasoconstriction in response to Ach in T group Unchanged in response to NTG in T group
		C: 9	Male	61±1				CFVR (adenosine)	↑In T group
Gielen *et al.*, 2003[28]	CAD	T: 10	Male	60.6±1.3	Hospital-based exercise training program: exercise under close supervision six times per day for 10 min on a bicycle ergometer at 80% of the heart rate reached at peak oxygen uptake (5 days per week) and one group training session per week including aerobic exercise, 9 calisthenics, and ball games	4	Angiography	luminal diameter (adenosine, Ach and NTG)	↑in response to Adenosine in T group ↓Vasoconstriction in response to Ach in T group Approximately unchanged in response to NTG
		C: 9	Male	60.1±2.2				CFVR (adenosine)	↑ in T group
Gielen *et al.*, 2003[28]	CAD	T: 10	Male	60.6±1.3	First four weeks Hospital-based exercise training program. 20-week home-based exercise training: training on a bicycle ergometer 20 min per day at 80% of their maximal heart rate (7 days per week). and one group training session per week including aerobic exercise, 9 calisthenics, and ball games	24	Angiography	luminal diameter (adenosine, Ach and NTG)	↑in response to adenosine in T group ↓ vasoconstriction in response to Ach in T group Approximately unchanged in response to NTG
		C: 9	Male	60.1±2.2				CFVR (adenosine)	↑In T group
Yoshinaga *et al.*, 2006[30]	CAD	T: 7	Male	61.9±4.2	Treadmill training at 60%-80% of the heart rate reserve, four sessions per week (two supervised and two unsupervised)	14	PET	CFVR (dipyridamole)	↑In T and C group. The T group showed a significantly greater % increase compared to C group in both normal and abnormal segments
		C: 5	Male	58.6±16.9					
Zbinden *et al.*, 2007[31]	CAD	T: 24	Male and female	61±8	Jogging or cycling at 80% of the heart rate at false three times/week for a duration of at least 60 min/session	12	Angiography	Luminal diameter (NTG)	↑ in T group
		C: 16						CFVR (adenosine)	↑ in T group
Bokhari *et al.*, 2019[32]	CAD	T: 9 C: 9	Male and female	63.7±9.7	Supervised exercise sessions three times per week. Each session lasted 45-60 min	12	PET	CFVR (adenosine)	↑ in T group

T=Training group, C=Control group, CFVR=Coronary blood flow velocity reserve, Ach=Acetylcholine, NTG=Nitroglycerin, PET=Positron emission tomography

In five studies (containing six trials), the effect of selected aerobic exercises was assessed on CFVR in response to adenosine and dipyridamole. A meta-analysis was performed, the results of which are shown in Figure 2a. All these trials were conducted on patients with CAD. As shown in the forest plot, aerobic exercise training improves the CFRV ($z = 3.15$, $P = 0.002$; SMD = 2.33, 95% CI: 0.88–3.78).

Table 2: Characteristics of quality score of studies

Studies	Reporting	External validity	Internal validity	Confounding and selection bias	Power	Quality score
Hambrecht *et al.*, 2000	7	3	5	4	3	22
Gielen *et al.*, 2003	7	2	5	4	3	21
Yoshinaga *et al.*, 2006	7	3	5	5	2	22
Zbinden *et al.*, 2007	8	2	6	5	4	25
Bokhari *et al.*, 2019	8	2	4	4	3	21

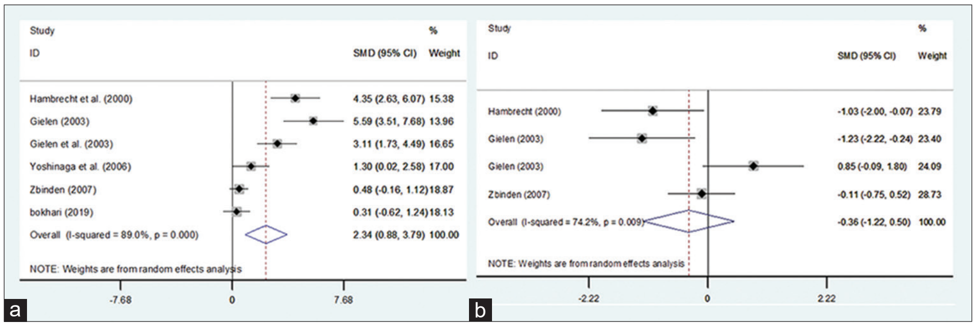

Figure 2: (a) Forest plot showing the effect of exercise on coronary blood flow velocity reserve. (b) Forest plot showing the effect of exercise on endothelium-independent vasodilator

In addition, high heterogeneity between studies had been reported ($\chi^2 = 45.26$, $P = 0.001$; $I^2 = 89\%$). Subgroup analyses showed significantly greater improvement in CFVR in studies with supervised exercise training program ($P = 0.04$) and more exercise sessions per week ($P = 0.02$) [Table 3]. In addition, meta-regression analyses demonstrated no significant relationships between sample size, year of publication, and quality score with CFVR [Figure 3].

Furthermore, in two studies, endothelium-dependent vasomotion was assessed using injections of various doses of acetylcholine. The results showed that a course of aerobic exercise increases the diameter of the lumen or decreases the contractile response of the lumen compared to preexercise condition.[28,29]

Vasodilatory response of coronary arteries in response to the endothelium-independent vasodilator nitroglycerin was investigated in three studies (containing four trials). A meta-analysis in this field shows that performing chronic aerobic exercises did not make a significant change in the endothelium-independent vasodilator ($z = 0.83$, $P = 0.40$; SMD = −0.36, 95% CI: −1.21–0.50) [Figure 2b], although a moderate heterogeneity was observed between studies ($\chi^2 = 11.65$, $P = 0.009$; $I^2 = 74.2\%$).

Due to the small number of studies in this field, it was not possible to perform subgroup analyses for many of the indices. Subgroup analyses showed nonsignificant differences across various groups [Table 4]. In addition, the meta-regression analyses demonstrated no significant relationships between sample size, year of publication, and quality score with endothelium-independent vasodilator [Figure 4].

According to the Begg's test ($z = 2.82$ and $P = 0.005$), publication bias was observed among the studies that reported CFVR [Figure 5a]. In addition, results of the Begg's test ($z = 1.36$ $P = 0.17$) demonstrated no publication bias in studies that reported endothelium-independent vasodilator [Figure 5b].

DISCUSSION

According to the findings of this study, coronary artery function in adaptation with exercise showed that a period of exercise leads to increased CFVR and improved endothelial function through stronger vasomotion response in the presence of pharmacological vasodilators.

The results showed more improvement in CFVR, in studies which exercise training was performed under supervision of supervisor. In addition, doing more exercise per week increased the CFVR further. However, the results showed that baseline CFVR, body mass index, and CFVR measurement had no effect on CFVR changes.

In the studies included in this systematic review, CFVR was evaluated using adenosine and dipyridamole. Adenosine is an endothelial-dependent vasodilator. Dipyridamole also increases adenosine and stimulates α-adrenergic receptors of smooth muscle. Increasing blood flow also increases endothelial-dependent vasodilation by shear stress. Thus, dipyridamole activates endothelial-dependent and -independent vasodilation responses.[30]

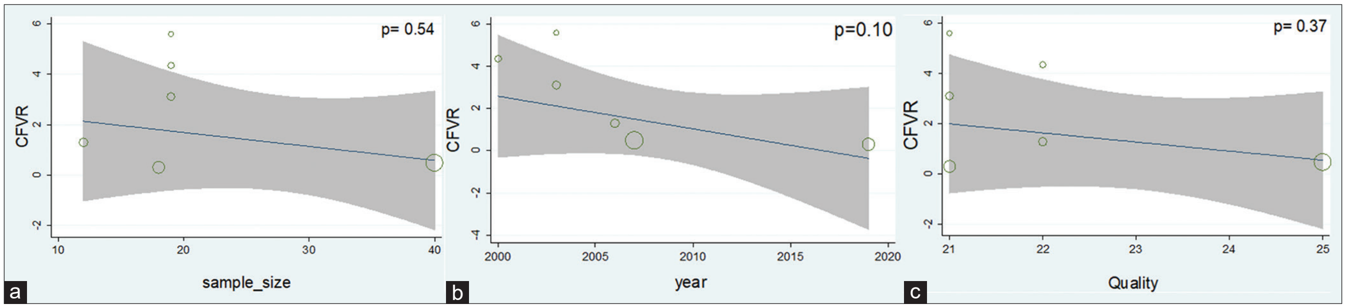

Figure 3: (a) Meta-regression analysis according to the sample size. (b) Meta-regression analysis according to the year of publication. (c) Meta-regression analysis according to the quality score

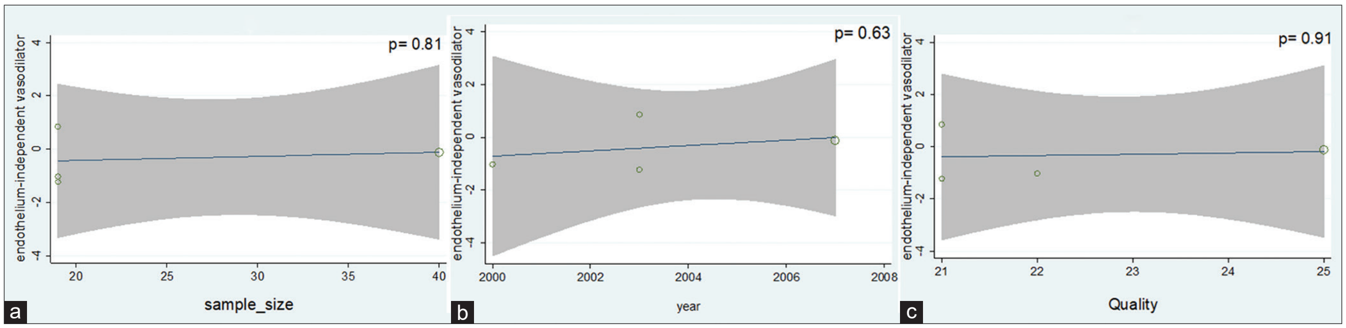

Figure 4: (a) Meta-regression analysis according to the sample size. (b) Meta-regression analysis according to the year of publication. (c) Meta-regression analysis according to the quality score

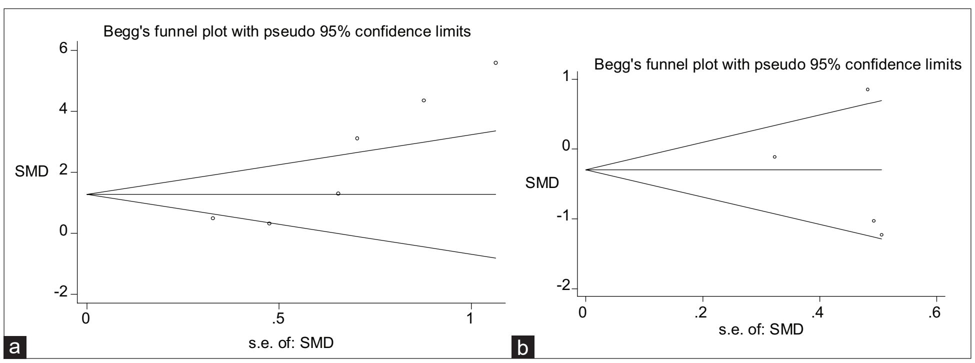

Figure 5: Funnel plot for report publication bias: (a) coronary blood flow velocity reserve and (b) endothelium-independent vasodilator

There was a nonsignificant decrease in the coronary artery response of patients with nitroglycerin. Considering that nitroglycerin is known as an endothelial-independent vasodilator, it can be concluded that aerobic exercises could not change the arterial smooth muscles' response.

The changes in nitric oxide levels, resulting from sports activities, seem to be the most important reason for CFVR changes. Increased oxygen demand during exercise, which leads to an increase in coronary blood flow and increase in shear stress and production of endothelial-derived relaxing factors; increase in NO that causes increase in cGMP and thus activate the calcium-activated K^+ channels and probably KATP channels that leads to relaxation of smooth muscle of vessel walls and increase in lumen diameter.[5-7]

As mentioned above, vessel vasomotion is dependent on the mechanisms and stimuli that regulate the synthesis and release of NO, while endothelial dysfunction in damaged blood vessels leads to decreased concentration of bioactive nitric oxide in the vascular smooth muscle cells.[33] Because pathophysiological changes occur in the pattern of coronary endothelial function in patients with CAD, it leads to paradoxical vasoconstriction in response to acetylcholine and further contraction of smooth muscle in the vessel wall at the time of catecholamine release during exercise.[28]

Another mechanism that seems to improve the blood flow in patients with CAD through physical activity is reducing the size of the injured area, the lesion.[34] Increasing the amount of catecholamines will also increase vascular contraction in

Table 3: Subgroup analyses of the effects of exercise on coronary blood flow velocity reserve

Subgroup(s)	Number of study	SMD (95% CI)	I^2%	*P*
Measurement				
Angiography	4	3.27 (0.82-5.71)	92.5	0.08
PET	2	0.70 (−0.24-1.65)	33.5	
Exercise training program				
Supervised	3	3.33 (−0.16-6.83)	93.6	0.04
Unsupervised	3	1.53 (0.02-3.05)	82.9	
Exercise sessions per week				
≥4	3	4.18 (2.79-5.57)	50.2	0.02
<4	3	0.55 (0.06-1.04)	0.0	
BMI				
<29	3	1.90 (−0.08-3.90)	88.5	0.12
≥29	3	2.88 (−0.02-5.79)	92.3	
Baseline CFVR				
<2.5	2	0.70 (−0.24-1.65)	92.5	0.06
≥2.5	4	3.27 (0.82-5.71)	3.5	

CFVR=Coronary blood flow velocity reserve, BMI=Body mass index, PET=Positron emission tomography, CI=Confidence interval, SMD=Standardized mean difference

Table 4: Subgroup analyses of the effects of exercise on coronary artery diameter after intracoronary nitroglycerin

Subgroup(s)	Number of study	SMD (95% CI)	I^2%	*P*
Exercise training program				
Supervised	2	−1.12 (−1.82-−0.43)	0.0	0.53
Unsupervised	2	0.30 (−1.21-0.49)	64	
BMI				
<29	2	−0.49 (−1.38-0.38)	58.8	0.71
≥29	2	−0.18 (−2.22-1.85)	88.8	

BMI=Body mass index, CI=Confidence interval, SMD=Standardized mean difference

the affected arteries; the reduction of this stimulator has been emphasized in adaptation to long-term aerobic exercises. Another factor influencing the flow rate is the reduced blood viscosity in adaptation to exercise, and thus increased flow.[35] Although some studies reported improvement in this index in patients with peripheral artery disease and healthy controls,[29] these changes have not been proven in patients with CAD or left ventricular dysfunction.[36]

The exercises included in the systematic reviews were all aerobic, but the method of exercises differed by continuous or interval methods, which could be the reason for the heterogeneity observed in findings, although separate meta-analysis of studies with different exercise methods was not possible, due to few number of studies.

This is the first meta-analysis study which examines the effect size of exercises on coronary artery vasomotor that provides reliable quantitative results using review and statistical methods to homogenize studies conducted over the past 30 years, as well as specific practical applications to patients and even researchers in this field.

Given that one of the meta-analysis objectives is to find research gaps, we can mention lack of studies examining the effectiveness of resistance exercises in patients with CAD. There is also lack of high-quality studies assessing various nonweight-bearing exercises (such as swimming) versus weight-bearing exercises or continuous versus interval exercises. On the other hand, in the present study, due to the small number of studies conducted, it was not possible to separate studies based on the patients' disease stages.

Although we tried to modify the effects of publication bias, to some extents, using statistical methods, this issue could affect the results of this meta-analysis, while small number of studies, based on valid databases and low sample size of studies included in the meta-analysis, can also play a role in the observed bias.

Considering that only articles published in English language were obtained from valid databases, publication and language bias would be of limitations of this study. In order to control multiple publication bias, all the numbers given in the text, tables, or figures of the similar (comparable) articles were examined.

CONCLUSION

Based on the results of the present study, aerobic exercises improve the endothelial function of coronary arteries and thereby the vascular vasomotion function, while the results of this meta-analysis showed no change in arterial smooth muscle's function by chronic aerobic exercises. Notably, there are insufficient studies examining the effectiveness of resistance exercises, which contrasts with new attitudes to resistance exercises.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Yang P, Wu P, Liu X, Feng J, Zheng S, Wang Y, *et al*. Interaction between eNOS gene polymorphism and current smoking on susceptibility to coronary heart disease in Chinese people. Coron Artery Dis 2020;31:87-91.
2. Tomanek R. Coronary Vasculature Development, Structure-Function, and Adaptations. New York: Springer; 2013.

3. Chan CL, Wang CW, Ho RT, Ho AH, Ziea ET, Taam Wong VC, *et al*. A systematic review of the effectiveness of qigong exercise in cardiac rehabilitation. Am J Chin Med 2012;40:255-67.
4. Brown MD. Exercise and coronary vascular remodelling in the healthy heart. Exp Physiol 2003;88:645-58.
5. Mann TN, Webster C, Lamberts RP, Lambert MI. Effect of exercise intensity on post-exercise oxygen consumption and heart rate recovery. Eur J Appl Physiol 2014;114:1809-20.
6. Letnes JM, Dalen H, Vesterbekkmo EK, Wisløff U, Nes BM. Peak oxygen uptake and incident coronary heart disease in a healthy population: The HUNT Fitness Study. Eur Heart J 2019;40:1633-9.
7. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. Physiol Rev 2008;88:1009-86.
8. Ross AJ, Gao Z, Pollock JP, Leuenberger UA, Sinoway LI, Muller MD. β-Adrenergic receptor blockade impairs coronary exercise hyperemia in young men but not older men. Am J Physiol Heart Circ Physiol 2014;307:H1497-503.
9. Nishikawa Y, Kanki H, Ogawa S. Role of nitric oxide in coronary vasomotion during handgrip exercise. Am Heart J 1997;134:967-73.
10. Gordon JB, Ganz P, Nabel EG, Fish RD, Zebede J, Mudge GH, *et al*. Atherosclerosis influences the vasomotor response of epicardial coronary arteries to exercise. J Clin Invest 1989;83:1946-52.
11. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary behavior, exercise, and cardiovascular health. Circ Res 2019;124:799-815.
12. Aengevaeren VL, Hopman MTE, Thompson PD, Bakker EA, George KP, Thijssen DHJ, *et al*. Exercise-induced cardiac troponin i increase and incident mortality and cardiovascular events. Circulation 2019;140:804-14.
13. Ashor AW, Lara J, Siervo M, Celis-Morales C, Oggioni C, Jakovljevic DG, *et al*. Exercise modalities and endothelial function: A systematic review and dose-response meta-analysis of randomized controlled trials. Sports Med 2015;45:279-96.
14. Anderson TJ. Assessment and treatment of endothelial dysfunction in humans. J Am Coll Cardiol 1999;34:631-8.
15. Widlansky ME, Gokce N, Keaney JF Jr., Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003;42:1149-60.
16. Beck EB, Erbs S, Möbius-Winkler S, Adams V, Woitek FJ, Walther T, *et al*. Exercise training restores the endothelial response to vascular growth factors in patients with stable coronary artery disease. Eur J Prev Cardiol 2012;19:412-8.
17. Gaglione A, Hess OM, Buechi M, Pucillo A, Krayenbuehl HP. Coronary tandem lesions: effect of exercise. Am Heart J 1992;123:1487-92.
18. Iantorno M, Hays AG, Schär M, Krishnaswamy R, Soleimanifard S, Steinberg A, *et al*. Simultaneous noninvasive assessment of systemic and coronary endothelial function. Circ Cardiovasc Imaging 2016;9:e003954.
19. Legallois D, Belin A, Nesterov SV, Milliez P, Parienti JJ, Knuuti J, *et al*. Cardiac rehabilitation improves coronary endothelial function in patients with heart failure due to dilated cardiomyopathy: A positron emission tomography study. Eur J Prev Cardiol 2016;23:129-36.
20. Anderson HV, Stokes MJ, Leon M, Abu-Halawa SA, Stuart Y, Kirkeeide RL. Coronary artery flow velocity is related to lumen area and regional left ventricular mass. Circulation 2000;102:48-54.
21. Hays AG, Iantorno M, Soleimanifard S, Steinberg A, Schär M, Gerstenblith G, *et al*. Coronary vasomotor responses to isometric handgrip exercise are primarily mediated by nitric oxide: A noninvasive MRI test of coronary endothelial function. Am J Physiol Heart Circ Physiol 2015;308:H1343-50.
22. Hambrecht R, Adams V, Erbs S, Linke A, Kränkel N, Shu Y, *et al*. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. Circulation 2003;107:3152-8.
23. Olsen RH, Pedersen LR, Jürs A, Snoer M, Haugaard SB, Prescott E. A randomised trial comparing the effect of exercise training and weight loss on microvascular function in coronary artery disease. Int J Cardiol 2015;185:229-35.
24. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.
25. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009. [Doi: 10.1136/bmj.b2700].
26. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52:377-84.
27. Nye C, Hahs-Vaughn D. Assessing methodological quality of randomized and quasi-experimental trials: A summary of stuttering treatment research. Int J Speech Lang Pathol 2011;13:49-60.
28. Gielen S, Erbs S, Linke A, Möbius-Winkler S, Schuler G, Hambrecht R. Home-based versus hospital-based exercise programs in patients with coronary artery disease: Effects on coronary vasomotion. Am Heart J 2003;145:E3.
29. Hambrecht R, Wolf A, Gielen S, Linke A, Hofer J, Erbs S, *et al*. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med 2000;342:454-60.
30. Yoshinaga K, Beanlands RS, Dekemp RA, Lortie M, Morin J, Aung M, *et al*. Effect of exercise training on myocardial blood flow in patients with stable coronary artery disease. Am Heart J 2006;151:1324.e11-8.
31. Zbinden R, Zbinden S, Meier P, Hutter D, Billinger M, Wahl A, *et al*. Coronary collateral flow in response to endurance exercise training. Eur J Cardiovasc Prev Rehabil 2007;14:250-7.
32. Bokhari S, Schneider RH, Salerno JW, Rainforth MV, Gaylord King C, Nidich SI. Effects of cardiac rehabilitation with and without meditation on myocardial blood flow using quantitative positron emission tomography: A pilot study. J Nucl Cardiol 2019. Online ahead of print.https://doi.org/10.1007/s12350-019-01884-9.
33. Gielen S, Schuler G, Hambrecht R. Exercise training in coronary artery disease and coronary vasomotion. Circulation 2001;103:E1-6.
34. Schuler G, Hambrecht R, Schlierf G, Niebauer J, Hauer K, Neumann J, *et al*. Regular physical exercise and low-fat diet. Effects on progression of coronary artery disease. Circulation 1992;86:1-1.
35. Ernst E. Influence of regular physical activity on blood rheology. Eur Heart J 1987;8 Suppl G: 59-62.
36. Reinhart WH, Dziekan G, Goebbels U, Myers J, Dubach P. Influence of exercise training on blood viscosity in patients with coronary artery disease and impaired left ventricular function. Am Heart J 1998;135:379-82.