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REVIEW

Acute and chronic effects of exercise on circulating endothelial progenitor cells in healthy and diseased patients

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Abstract Exercise is known to improve endothelial function in healthy subjects as well as patients with cardiovascular disease and this might be partially related to a regeneration of diseased endothelium by circulating progenitor cells (EPCs). EPCs are a subgroup of peripheral blood monocytes that contribute to re-endothelialization of injured endothelium as well as neovascularization of ischemic lesions. Cross-sectional studies have indicated that chronic, regular physical activity has a positive effect on the levels of circulating EPCs. This is associated with an improvement of endothelial dysfunction that is induced by apoptosis due to the underlying aging process or accelerated by cardiovascular risk factors. Furthermore, it is well established that chronic exercise training has the potency to mobilize EPCs from the bone marrow. For patients with cardiac disease this is of clinical importance since EPCs have been implicated in vascular repair and revascularization. Studies are needed to refine the best mode of exercise training that will upregulate circulating EPCs as well as to clarify the kinetics of EPCs after the termination of different exercise sessions in different diseases and medication. Whether there is a direct link between enhanced mobilization of EPCs via exercise and improvement of disease and prognosis remains a hypothesis which needs to be further evaluated.

Keywords Endothelial progenitor cells · Acute exercise · Chronic exercise

Introduction

Systematic exercise is associated with favorable adaptations in body composition, lipid and glucose metabolism, blood coagulation and inflammation markers, blood pressure, and autonomic tone. These factors all influence the integrity of the vascular endothelium, a plausible explanation for the cardioprotective benefits of exercise training [1–4].

The endothelium is the crucial compartment between circulating metabolic risk factors and the development of atherosclerosis. Impairment of the endothelial function is caused by cardiovascular risk factors and is associated with subsequent cardiovascular events [5].

Regeneration of injured endothelium resides from cells within the vessel wall, but has been also attributed to circulating cells derived from the bone marrow. This bone marrow-derived cell population was identified as endothelial progenitor cells (EPCs) in the late 1990s [6]. The number of systemically circulating EPCs can be increased by several stimuli, including drugs and lifestyle modification [7–9].

During the last decade several studies have demonstrated that acute and chronic exercise training has the potency to mobilize EPCs from the bone marrow. This has been attributed to be important for regeneration of the endothelial cell layer and revascularization, partially explaining the beneficial effects of exercise. This review

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will briefly discuss the acute and chronic effects of exercise on endothelial progenitor cells in healthy individuals as well as in patients with cardiovascular disease providing recent scientific knowledge.

Definition and role of EPCs

In 1997, Asahara and co-workers [6] identified bone marrow-derived circulating EPCs from the bloodstream and established their regenerative potential regarding angiogenesis and vascular repair. However, until today the proper isolation and quantification technique of EPCs is still a matter of debate. The method most often used is flow cytometry using specific antibodies against specific cell surface markers such as CD34, CD133 and vascular endothelial growth factor 2 (VEGFR2 or KDR). The combination of CD34+/KDR+ is the most often set used for the quantification of EPCs in the relevant literature [8, 10].

Using the cell culture method two types of EPCs (early and late outgrowth cells) with different morphology, proliferation rates survival behaviors have been identified. Despite such differences they equally contributed to neovasculogenesis in vivo in that early EPCs secreted angiogenic cytokines, whereas late EPCs supplied a sufficient number of endothelial cells. Early EPCs often referred to as circulating angiogenic cells (CACs) [11, 12]. Another approach to quantify EPCs is the use of colony forming cell assays where EPC colony-forming units were cultured and counted (for more detailed explanation regarding EPCs characterization see Refs. [11, 12]).

There is evidence that EPCs contribute to re-endothelialization of injured endothelium as well as neovascularization of ischemic lesions [10]. This seems to have clinical impact as well. In patients with cardiovascular risk factors, high levels of circulating progenitor cells are associated with event-free survival from cardiovascular events, whereas a decrease in the number of EPCs seems to be an independent predictor of morbidity and mortality of cardiovascular diseases [13, 14]. These findings suggest that regulation of the number and function of EPCs may directly influence the maintenance and development of atherosclerosis (Fig. 1).

The relationship between the circulating EPCs and atherosclerosis is not completely understood since a limited number of studies reported increased levels of EPCs in patients with acute myocardial infarction and unstable ischemic syndromes [15, 16]. Significant improvements, however, after intracoronary infusion of autologous bone marrow mononuclear cells were reported in exercise capacity and myocardial perfusion in patients with end-stage ischemic cardiomyopathy [17] as well as an improved recovery of left ventricular function in patients after acute myocardial infarction [18]. Thus, enhancement of EPCs is considered one of the most promising healing alternatives for cardiovascular disease and exercise appears to be helpful in achieving this therapeutic target.

Cross-sectional studies and levels of EPCs

Compared to sedentary subjects, trained individuals have up to 4-fold higher progenitor cell counts [19, 20] and the positive impact of physical fitness seems to extend in various diseased populations. Luk and co-workers [21] assessed the impact of habitual physical activity level (PAL) on vascular endothelial function and circulating EPCs in 166 patients (aged 67.8 ± 9.5 years) with stable

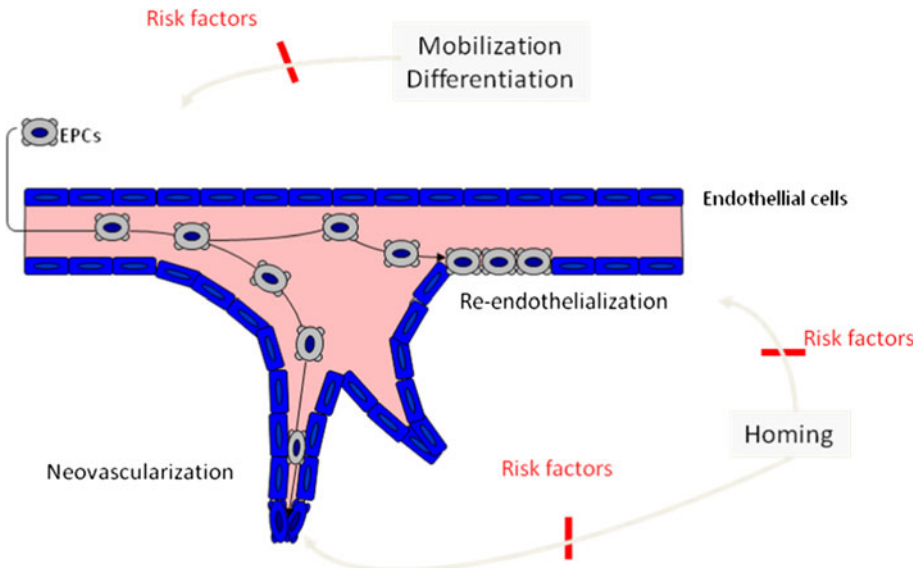

Fig. 1 Role of EPCs in re-endothelialization and neovascularization after injury

CAD and preserved left ventricular ejection fraction (EF ≥45 %). In their study, patients with the highest tertile of PAL had higher levels of CD133/KDR+ EPCs by 44 % ($p = 0.01$) compared with those in the lowest tertile, after adjusting for age, sex, presence of hypertension, diabetes mellitus, hypercholesterolemia, smoking, and the use of medications including statins. Another cross-sectional study [22] reported that in both young (21–33 years old) and older men (59–72 years old), the number of circulating EPCs was greater in endurance-trained than in sedentary men. The age-related decline in endurance-trained men (24 and 29 %, respectively) was smaller ($p < 0.05$) than that in sedentary older men (50 and 43 %, respectively). The same pattern was observed for the migratory and proliferative activities of circulating EPCs, indicating that regular exercise can attenuate the age-related decline in activity of circulating EPCs in healthy men.

In a group of hemodialysis patients, Manfredini and co-workers [23] tested whether the mobilization of EPCs was related to the degree of exercise capacity as assessed by the distance walked in the 6-min walking test and the maximal speed attained in an incremental treadmill test. Multivariate analysis indicated 6-min walking distance as the most significant independent factor associated with EPC level. EPC percentage value was significantly lower ($p = 0.009$) in the worse (<300 m) than in the better performing group (>300 m). Based on the above cross-sectional data, those individuals who performed chronic, regular physical activity seems to have higher levels of circulating EPCs, thereby improving endothelial dysfunction that is induced by apoptosis due to the underlying aging process or accelerated by cardiovascular risk factors.

Acute exercise responses on EPCs

In 2004, Rehman and co-workers [24] were among the first who investigated whether a single episode of exercise could acutely increase the numbers of EPCs and cultured/CACs in patients, aged 54 ± 10 years, with chronic disease manifestations such as diabetes, hypertension and hyperlipidemia. In their study, circulating EPCs increased nearly 4-fold in peripheral blood (from 66 ± 27 to 236 ± 34 cells/ml, $p < 0.05$), whereas the number of isolated CACs increased 2.5-fold (from 8.7 ± 2.0 to 20.7 ± 4.6 cells/ml, $p < 0.05$) in response to a symptom-limited exercise stress test.

In another study, blood concentration of EPCs was analyzed in CAD patients with or without exercise-induced myocardial ischemia and in healthy subjects for up to 144 h after maximal stress test [25]. All participants were non-obese with normal left ventricular function (EF ≥60 %) and their age ranged between 59–65 years. EPCs increased significantly in ischemic patients, with a maximum after 24–48 h and returned to baseline within 72 h. In non-ischemic patients and healthy subjects, no EPC increase was detectable. In the same study VEGF levels increased significantly after 2–6 h only in the ischemic patients. Furthermore, the changes in VEGF and EPCs concentrations correlated significantly ($r = 0.66$). In a relevant study, Sandri and co-workers [26] assessed the role of acute ischemia for EPC mobilization in two different populations. Twenty-three patients (aged 61.4 ± 2.1 years) with peripheral arterial occlusive disease (PAOD) performed a maximal treadmill test with exercise-induced ischemia, whereas 17 healthy volunteers, aged 31.3 ± 3.4 years, underwent a 15-min suprasystolic occlusion of one lower extremity. EPCs increased significantly in both PAOD patients from 82 ± 20 to 256 ± 52 ($p < 0.05$) and healthy subjects from 144 ± 39 to 590 ± 61 cells per 1 million events ($p < 0.05$) in response to induced ischemia, with a maximum after 24 h and returned to baseline within 72 h.

In addition, Laufs and co-workers [27] compared the effects of three different running protocols on the number and function of circulating EPCs in moderately endurance-trained students (age 28.4 ± 6.5 years, VO_{2max} 57.8 ± 2.7 ml/kg/min). The volunteers underwent 3 controlled running protocols on a 400-m track in a random order defined as: 30 min at 82 % VO_{2max}, 30 min at 68 % VO_{2max} and 10 min at 68 % VO_{2max}. Both 30-min protocols (intensive and moderate running) increased circulating EPC numbers to 235 ± 93 and 263 ± 106 % of control levels, respectively. However, moderate short-term running for 10 min did not upregulate EPC counts suggesting that exercise intensity is a critical factor for EPCs mobilization.

Recently, Van Craenenbroeck and co-workers [28] assessed the effect of an acute symptom-limited exercise test on functional characteristics of CACs and numbers of circulating CD34+ and CD34+/KDR+ progenitor cells in sedentary patients with mild and severe CHF (EF 23–32 %). They found that cardiopulmonary exercise testing improved CAC migration in severe (+52 %, $p < 0.05$) and mild CHF (+31 %, $p < 0.05$), restoring it to levels similar to controls. Based on the above, the majority of the studies demonstrated so far that acute exercise in disease or healthy individuals has the capacity to increase the release of EPCs primarily from the bone marrow (Table 1) [23–31].

However, age, health and training status may modify the acute exercise effects on EPCs. Thijssen and co-workers [32] found that the acute exercise-induced increase in circulating EPC number was greater in younger than older men, whereas Jenkins and co-workers [33] reported a significant increase in EPC colony-forming units following 30 min of running at 75 % VO_{2max} in highly active, but not

Table 1 Acute responses of exercise on EPCs in healthy individuals and patients with cardiovascular disease

Study	*n*/age	Health status	Training status (VO_{2max})	Exercise program	Major findings
Healthy					
Laufs et al. [27]	25/28	Healthy	Moderately trained (57.8 ml/kg/min)	Three different exercise protocols 30 min at 82 %; 30 min at 68 %; 10 min at 68 % of VO_{2max})	Significant increases in EPCs only after the 30-min protocols (+235 and +263 %, respectively)
Ciulla et al. [37]	1/44	Healthy	Moderately trained (45.2 ml/kg/min)	20-day stay at a mean of 3,900 m in the Himalayas	Fivefold increase 1 day after the trek in the EPCs population (20.49 vs. 4.88 cells/μl); complete normalization at sea level 45 days after
Morici et al. [38]	20/17	Healthy	Competitive rowers (56.5 ml/kg/min)	Supramaximal all-out rowing over 1,000 m	Significant increases in EPCs by 114.5 %
Yang et al. [29]	16/25	Healthy	Not reported	Maximal stress testing	EPCs enhanced +66.6 % and their migratory activity +57.8 %
Van Craenenbroeck et al. [31]	11/24 14/36	Healthy Healthy	Moderately trained (50.6 ml/kg/min) Moderately trained (46.0 ml/kg/min)	Maximal cardiopulmonary stress testing	Significant increases in EPCs in both groups (+76 and +69 %, young vs. old)
Goussetis et al. [35]	10/43	Healthy	Highly trained (–)	Ultra marathon race of 246 km (Spartathlon)	Significant increases in EPCs by 11-fold at finishing
Thorell et al. [30]	13/24–47	Healthy	Moderately trained (–)	1 h bicycle spinning session	Significant increases in late outgrowth EPCs (+100 %) 1 h after the session
Moebius-Winkler et al. [36]	18/32	Healthy	Highly trained (60 ml/kg/min)	4 h at 70 % of IAT	Significant increases in both CD34+/KDR+ cells (5.5-fold) and CD133+/KDR+ cells (3.5-fold) after finishing cycling
Bonsignore et al. [39]	10/44	Healthy	Amateur runners (–)	Subjects underwent a marathon race and a 1.5 km field test	Significant increases in CFU-EC only after the 1.5 km field test (+140 %)
Diseased					
Adams et al. [25]	16/65 12/60 11/59	Ischemic CAD Non-ischemic CAD Healthy	– – –	Maximal stress testing	Significant increases in EPCs (+164.0 %) up to 6 h after exercise only in the ischemic patients
Rehmann et al. [24]	22/54	Chronic disease	Sedentary	Symptom-limited exercise stress test until 90 % of HR_{peak}	Significant increases in EPCs (+258 %) and CACs (+138 %)
Van Craenenbroeck et al. [28]	22/62 19/63 13/56	Mild CHF Severe CHF Healthy	Sedentary Sedentary Sedentary	Maximal cardiopulmonary stress testing	No significant change in circulating EPCs; however improvements in CACs migratory capacity only in CHF pts (increase of 52 vs. 31 % in severe vs. mild CHF)
Sandri et al. [26]	23/61 17/31	PAOD Healthy subjects	Not reported Not reported	Patients underwent a maximal treadmill test; healthy subjects A 15-min suprasystolic occlusion of the lower extremity	Significant increases in EPCs in both PAOD patients (+212.2 %) and healthy subjects (+309.7 %)

CACs circulating angiogenic cells, *CFU-EC* colony forming units-endothelial cell, *CVRF* cardiovascular risk factors, *EPCs* endothelial progenitor cells, *IAT* individual anaerobic threshold, HR_{peak} heart rate peak, *PAOD* peripheral arterial occlusive disease

in low-active, young healthy men. In most of the studies which examined the effects of acute exercise on the amount of EPCs, the participants performed a maximal cardiopulmonary exercise test.

However, analyzing the impact of longer and more strenuous exercise (like a marathon or spartathlon race) no conclusive data exist [19, 34–36]. In advanced-age runners, aged 57 ± 6 years, Adams and co-workers [34] reported a significant inflammatory response and downregulation of circulating hematopoietic stem cells after finishing a marathon race (CD34+ cells 1.829 ± 115 vs. 1.175 ± 75 cells/ml). In a relevant published study by Goussetis and co-workers [35], EPCs increased by nearly 11-fold (from 44.5 ± 2.5 to 494.6 ± 27.9 cells/ml) and remained elevated at 48 h after a 246-km race in healthy middle aged runners (42.8 ± 1.4 years). In an interesting case study, Ciulla and co-workers [37] assessed the response of EPCs after a 20-day stay of a 44-year-old male at a mean of 3,900 m in the Himalayas. They reported a 5-fold increase 1 day after the trek in the EPCs population (20.49 vs. 4.88 cells/ml), whereas a complete normalization at sea level after 45 days was observed.

In two other studies the release of progenitor cells after very intense exercise was also studied [38, 39]. In the study of Morici and co-workers [38], supramaximal exercise doubled circulating CD34+ cells (7.6 ± 3.0 vs. 16.3 ± 9.1 cells/μl) after a 1,000 m, "all-out effort" in young competitive rowers, whereas in the study of Bonsignore and co-workers [39], significant increases (+140 %) in EPC colony-forming units after a 1,500 m maximum field test was reported.

The above data further suggest that the EPCs response may vary according to the intensity and duration of the exercise protocols. According to the type of exercise, no data are available so far on the effects of resistance exercise protocols on EPC number and function and this issue needs to be clarified in further studies.

Chronic adaptations of exercise on EPCs

Several studies during the last decade have examined the alterations in the number and function of circulating EPCs after long-term exercise training. Laufs and co-workers [40] conducted the first basic, randomized study where mice underwent voluntary running for 28 days; for the same period 19 patients with documented CAD followed a controlled, standardized exercise program. Numbers of EPCs of trained mice were enhanced to 267, 289, and 280 % of control levels after 7, 14, and 28 days, respectively. Furthermore, running inhibited neointima formation after carotid artery injury by 22 % and increased neoangiogenesis by 41 % compared with controls. In the same study, patients with stable coronary artery disease experienced significant increases in circulating EPCs (+78 %, $p < 0.05$) and reduced the rate of EPC apoptosis (−41 %, $p < 0.05$). In agreement with the previous study, Steiner and co-workers [41] found a significant increase in circulating EPCs (2.9 ± 0.4-fold increase) after 12 weeks of supervised aerobic training in patients with documented CAD, which was positively correlated with the change of FMD ($r = 0.81$) and the increase of NO synthesis ($r = 0.83$).

Hoetzer and co-workers [20] reported that regular exercise can increase both EPC colony-forming units and migratory capacity in previously sedentary middle aged men. In their study, the number of EPC colonies doubled from 10 ± 3 to 22 ± 5 cells/ml, and migratory activity increased by 49.6 % (from 683 ± 96 to 1.022 ± 123 RFUs) 3 months after aerobic training. Recently, Sonnenschein and co-workers [42] evaluated the effects of moderate exercise training on in vivo endothelial repair capacity of early EPCs, and their nitric oxide and superoxide production in subjects with metabolic syndrome. Exercise training resulted in a substantially improved in vivo endothelial repair capacity of early EPCs (24.0 vs. 12.7 %; $p < 0.05$) and improved endothelium-dependent vasodilation. Moreover, nitric oxide production of EPCs was substantially increased after exercise training with a parallel reduction in superoxide production.

Of particular interest are the alterations on EPCs caused by exercise training in patients with heart failure who have impaired endogenous endothelial regenerative capacity. Sarto and co-workers [43] reported a 251 % increase in CD34+/KDR+EPC levels in patients with CHF (EF 30.5 % and peak VO_2 15.1 ml/kg/min) in response to 8 weeks of supervised aerobic training, whereas lower improvements in the EPCs count (+80 %) were found after a shorter training period of 3 weeks [44]. Even, in patients with advanced heart failure (EF 24 ± 2 % and NYHA IIIb), Erbs and co-workers [45] recently demonstrated that 12 weeks of endurance training increased the number of EPCs by 83 % and their migratory capacity by +224 %; this was associated with an augmentation in ejection fraction and skeletal muscle neovascularization.

Based on the above observations, long-term aerobic exercise significantly improves the number of circulating EPCs and their migratory capacity (Table 2) [40–47] in healthy subjects and patients with cardiovascular disease/heart failure alike.

Mechanisms of the exercise-induced alterations on the levels of EPCs

The mechanisms by which exercise increase the number and function of EPCs are not fully understood. The

Table 2 Summary of studies examining the chronic effects of exercise training on EPCs

Study	*n*/age	Condition	Duration/ frequency	Intensity/type of training	Major findings
Laufs et al. [40]	12–16/–	Animal subjects	3 weeks/5	30 min with 12 m/min/ aerobic	EPCs enhanced +267, +289 and +280 % after 7, 14, and 28 days of training
Laufs et al. [40]	19/70	CAD	4 weeks/–	15–20 min at 60–80 of VO_{2peak}/aerobic	EPCs increased by 78 %; reduced apoptosis rate by 41 %
Sandri et al. [47]	9/57	PAOD	4 weeks/5	Not reported/aerobic training	Significant increases in EPCs by 440 % only in PAOD pts
	9/63	Prior PAOD	4 weeks/5		
	15/61	CAD	4 weeks/5		
Steiner et al. [41]	20/52	CAD/CVRF	12 weeks/3	Not reported/cardiovascular training	2.9-fold increase in EPCs which was positively correlated with the change of FMD and the increase of NO synthesis
Thijssen et al. [32]	8/67–76	Sedentary	8 weeks/3	20 min at 65–85 % of HRR/aerobic	No significant alterations on EPCs after training
Hoetzer et al. [20]	10/59	Sedentary	12 weeks/5–7	40–50 min at 60–75 % of HR_{max}/aerobic	CFU-EC enhanced +120 %; migratory activity +49.6 %
Sarto et al. [43]	22/61	Heart failure (EF 30.5 %)	8 weeks/3	55 min at 60 % of HRR/ aerobic	EPCs enhanced +251 % and CFU-EC + 267 %
Cesari et al. [46]	86/73	CAD/VHD	12 weeks/6	Not reported/aerobic	Only pts with a median improvement >23 % of 6 MWT showed a significant increase of EPCs by 88.2 %
Gatta et al. [44]	14/72	Heart failure (EF 34 %)	3 weeks/2 × 6	30 min at 75–85 % of HR_{max}/aerobic	EPCs enhanced +80 % and CFU-EC + 51.3 %
Erbs et al. [45]	18/60	Heart failure (EF 24 %)	3 weeks/3–6 12 weeks/daily	5–20 min at 50 % of VO_{2max}/aerobic 20–30 min at 60 % of VO_{2max}/aerobic	EPCs enhanced +83 %; migratory activity +224 %
Sonnenschein et al. [42]	12/58	Metabolic syndrome	8 weeks/5	30 min at 50–70 % of VO_{2max}	EPCs enhanced +27.9 % and in vivo endothelial repair capacity +24 %

CAD coronary artery disease, *CFU-EC* colony forming units-endothelial cell, *CVRF* cardiovascular risk factors, *EF* ejection fraction, *EPCs* endothelial progenitor cells, HR_{max} heart rate maximum, *HRR* heart rate reserve, *NO* nitric oxide, *pts* patients, *VHD* valve heart disease

increases in blood flow and hemodynamic alterations that occur during exercise (shear stress) is a potent stimulus for the increased NO production via increased activity of endothelial nitric oxide synthase (eNOS). The importance of NO for the exercise-induced release of EPCs was supported by the analysis of eNOS knockout mice in the study of Laufs and co-workers [40] who demonstrated that mice lacking eNOS did not show an augmented EPC mobilization after exercise.

Another important humoral factor for EPCs mobilization is VEGF; its role for stimulating the release of EPCs has been confirmed in animal and human studies. Exercise causes cellular hypoxia and leads to a hypoxia-inducible factor-1-mediated upregulation of VEGF and other growth factors [48], which stimulate EPC mobilization (Fig. 2).

In addition, the increased oxidative stress that characterizes patients with cardiovascular disease results in a decline in NO bioavailability. Exercise training, however, has the potential to restore the balance between NO production and inactivation by reactive oxygen species improving thereby vascular repair capacity [49]. Furthermore, the reduced EPC number of patients with advanced cardiovascular disease (heart failure) is often due to the myelosuppressive effects of TNF-α [50]. It is well known that exercise causes anti-inflammatory adaptations; thus the reduction of TNF-α and other cytokines might also explain the increase in EPC number and function as a result of systematic training. Irrespective of an upregulation of EPC generation, physical exercise may increase EPC numbers indirectly by prolonging their lifespan [42]. Further research is required to fully clarify the exact molecular pathways that could explain the exercise-induced beneficial adaptations on EPCs which lead to improved endothelial health and reduced cardiovascular risk.

Clinical implications

Since the process of atherosclerosis can begin in the childhood period, enhancement of EPCs by exercise seems to be essential for an effective early prevention of cardiovascular disease. Indeed, even in high school children the positive impact of exercise on EPCs has been confirmed after 1 year of an intense exercise program [51].

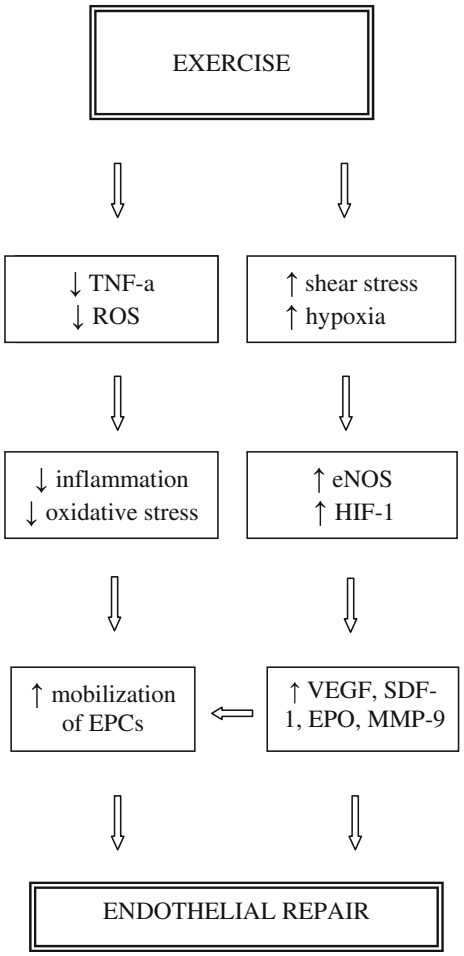

Fig. 2 Possible mechanisms of exercise-induced alterations on EPCs

Furthermore, endothelial dysfunction is the hallmark of vascular damage with advancing age and the decline in function and number of circulating EPCs leads to increased cardiovascular risk. Therefore, improving re-endothelialization capacity by EPCs via exercise training may be directly linked to reduced cardiac morbidity or even mortality.

Conclusions and future directions

According to recent scientific knowledge, exercise leads to acute increases in circulating EPCs that may maintained for up to 2–3 days past sessions' termination with exercise intensity to be a crucial factor for this mobilization. Furthermore, systematic, chronic exercise has the potency to mobilize EPCs from the bone marrow in both healthy and diseased individuals. Given the ability of these cell populations to promote vascular regeneration and angiogenesis, this may be an important mechanism in the prevention and treatment of atherosclerosis and cardiovascular disease.

However, several issues need further investigation. In the majority of the acute studies the participants performed a maximal cardiopulmonary exercise test; this, however, does not reflect real training routines. According to current knowledge, we advise patients to train aerobically at 60–70 % of VO_{2peak} for 30–45 min. In order to induce a sufficient EPC-mediated vascular protection, exercise must be uninterrupted throughout life with a frequency of 3–4 times per week. Since exercise intensity is an important factor for EPCs mobilization and if tolerated, patients should also perform high-intensity interval exercise up to 90 % of VO_{2peak}. Recent studies indicated that this kind of training seemed to be more effective than moderate intensity training in patients with CAD and CHF [52–54]. There is a need, however, for exact information regarding intensity and duration in order to refine the best exercise protocol that will upregulate circulating EPCs as well as better determine their kinetics after the termination of different exercise sessions. Furthermore, it is unknown whether other exercise modalities such as resistance training could also affect EPCs mobilization (both in health and disease) and further research is required on this topic.

One of the major challenges of the near future is to resolve how EPCs lead to a repair and maintenance of an intact endothelial cell layer. Two scenarios for this have been recently proposed by Lenk and co-workers [55]. The first refers to homing to the damaged endothelial cell layer via a specific receptor and the second states that the circulating EPCs stimulated the proliferation of mature endothelial cells via the secretion of growth factors. Direct proof of the above is still vague and future studies have to investigate the exact molecular mechanisms by which exercise and other life-style modalities determine the process of endothelial repair and neovascularization by EPCs. This will be of scientific as well as clinical interest to prevent and treat cardiovascular disease by life-style intervention.

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