World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/esps/
wjc@wjgnet.com
doi:10.4330/wjc.v4.i12.312

World J Cardiol 2012 December 26; 4(12): 312-326
ISSN 1949-8462 (online)

EDITORIAL

Circulating endothelial and progenitor cells: Evidence from acute and long-term exercise effects

Matina Koutroumpi, Stavros Dimopoulos, Katherini Psarra, Theodoros Kyprianou, Serafim Nanas

Matina Koutroumpi, Stavros Dimopoulos, Serafim Nanas, Cardiopulmonary Exercise Testing and Rehabilitation Laboratory, 1st Critical Care Medicine Department, Evangelismos Hospital, National and Kapodistrian University of Athens, 10676 Athens, Greece
Katherini Psarra, Department of Immunology, Evangelismos Hospital, 10676 Athens, Greece
Theodoros Kyprianou, Critical Care Department, Nicosia General Hospital, 2029 Nikosia, Cyprus
Author contributions: Koutroumpi M wrote the first draft; Dimopoulos S contributed to the first draft and revised the manuscript; Psarra K and Kyprianou T revised the manuscript; and Nanas S gave the final review.
Correspondence to: Stavros Dimopoulos, MD, Cardiopulmonary Exercise Testing and Rehabilitation Laboratory, 1st Critical Care Medicine Department, Evaggelismos Hospital, National and Kapodistrian University of Athens, 10676 Athens, Greece. a-icu@med.uoa.gr
Telephone: +30-697-3956974 Fax: +30-213-2041888
Received: August 30, 2012 Revised: October 31, 2012
Accepted: November 6, 2012
Published online: December 26, 2012

Abstract

Circulating bone-marrow-derived cells, named endothelial progenitor cells (EPCs), are capable of maintaining, generating, and replacing terminally differentiated cells within their own specific tissue as a consequence of physiological cell turnover or tissue damage due to injury. Endothelium maintenance and restoration of normal endothelial cell function is guaranteed by a complex physiological procedure in which EPCs play a significant role. Decreased number of peripheral blood EPCs has been associated with endothelial dysfunction and high cardiovascular risk. In this review, we initially report current knowledge with regard to the role of EPCs in healthy subjects and the clinical value of EPCs in different disease populations such as arterial hypertension, obstructive sleep-apnea syndrome, obesity, diabetes mellitus, peripheral arterial disease, coronary artery disease, pulmonary hypertension, and heart failure. Recent studies have introduced the novel concept that physical activity, either performed as a single exercise session or performed as part of an exercise training program, results in a significant increase of circulating EPCs. In the second part of this review we provide preliminary evidence from recent studies investigating the effects of acute and long-term exercise in healthy subjects and athletes as well as in disease populations.

Key words: Circulating endothelial cells; Circulating progenitor cells; Exercise; Cardiovascular disease

Peer reviewers: Jesus Peteiro, MD, PhD, Unit of Echocardiography and Department of Cardiology, Juan Canalejo Hospital, A Coruna University, A Coruna, P/ Ronda, 5-4º izda, 15011 A Coruña, Spain; Dr. Thomas Hellmut Schindler, Department of Medecine, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil, 4, 1211 Geneva, Switzerland

Koutroumpi M, Dimopoulos S, Psarra K, Kyprianou T, Nanas S. Circulating endothelial and progenitor cells: Evidence from acute and long-term exercise effects. *World J Cardiol* 2012; 4(12): 312-326 Available from: URL: http://www.wjgnet.com/1949-8462/full/v4/i12/312.htm DOI: http://dx.doi.org/10.4330/wjc.v4.i12.312

CIRCULATING ENDOTHELIAL AND PROGENITOR CELLS

The process of blood vessel formation occurs by two different mechanisms, angiogenesis and vasculogenesis. Angiogenesis describes blood vessel growth from existing blood vessels by sprouting of differentiated endothelial cells or intussusceptions of existing capillaries[1,2]. In contrast, vasculogenesis is defined as blood vessel

growth from *in situ* differentiating angioblasts[3]. Until recently, it has been assumed that vasculogenesis is limited to embryogenesis. For the first time in 1997, Asahara *et al*[4] described the existence of endothelial cells in the peripheral blood of adults derived from the bone marrow, and confirmed the role of vasculogenesis during the process of postnatal neovascularization. Hematopoietic stem cells that give rise to blood cells and move between bone marrow and peripheral blood are the best-characterized adult stem cells in humans. This circulating bone-marrow-derived cell population has been named endothelial progenitor cells (EPCs)[5]. There are at least two different types of EPCs population, early and late. Early EPCs are usually referred to as the angiogenic EPC population obtained from short-term cultures of 4-7 d. Late EPCs, often called outgrowth EPCs, have different growth patterns and are usually obtained from long-term cultures of at least 2-4 wk[6]. These cells are capable of maintaining, generating, and replacing terminally differentiated cells within their own specific tissue as a consequence of physiological cell turnover or tissue damage due to injury[7].

Endothelial cell injury, after tissue ischemia or vascular injury, initiates physiological processes of reparation and regeneration. The initial step is the mobilization of EPCs from the bone marrow into peripheral blood, which is followed by the recruitment of EPCs to the site of tissue ischemia or vascular injury (Figure 1). Locally, vasculogenesis occurs after EPC adhesion and migration into the newly formed vascular network and differentiation into mature endothelial cells[8]. The pathophysiology mentioned above is critical in terms of endothelium maintenance and restoration of normal endothelial cell function.

The current literature suggests that adult stem cells generate differentiated cells beyond their own tissue boundaries, a process termed "developmental plasticity". Circulating EPCs play two major roles, endothelial healing and neoangiogenesis[9,10].

EPCs AND ENDOTHELIAL DYSFUNCTION

For more than 10 years researchers as well as clinicians have focused on understanding the physiological and pathophysiological role of the EPCs in the cardiovascular system and in cardiovascular disease, because endothelial dysfunction has been established as an independent prognostic risk factor for cardiovascular disease[11,12]. Although there are no clear definition criteria for accurate identification of EPCs so far, there have been several studies indicating the important role of EPCs in restoring endothelial damage[13]. Decreased numbers of EPCs have been associated with endothelial dysfunction and high cardiovascular risk[5,14].

Promotion of recruited bone-marrow-derived EPCs is the primary mechanism for endothelial replacement in areas of vascular damage as demonstrated in animal models. In these experimental ischemic injuries, bone-marrow-derived cells play an important role in vascular repair and regeneration enhancing tissue recovery[15-17].

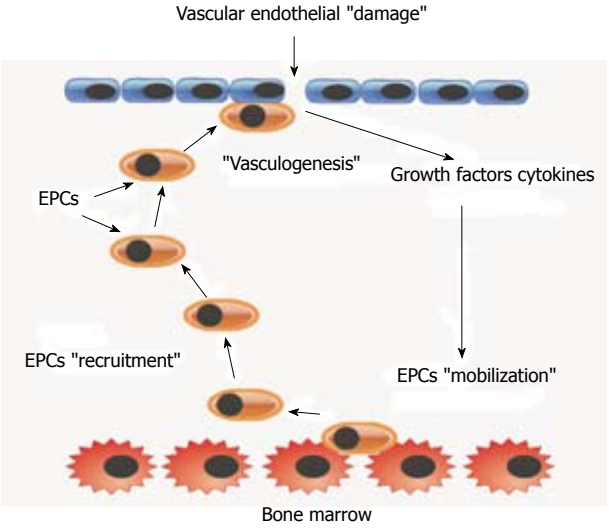

Figure 1 An illustrative model of vasculogenesis after vascular endothelial damage mediated by bone marrow endothelial progenitor cell mobilization and recruitment. EPC: Endothelial progenitor cell.

EPCs are present in peripheral blood circulation of healthy adult subjects, although in small numbers and are responsible for vascular and endothelial repair after tissue damage[18]. A decrease in EPC levels was shown to inversely correlate with the occurrence of endothelial dysfunction[5,19].

EPCs AND AGING

It has been also documented that EPCs are significantly reduced in elderly populations[20], and appear to have elevated apoptotic susceptibility[21]. The number and function of early EPCs isolated from the peripheral blood of 20 healthy young and 20 old (61 ± 2 years) individuals have been investigated by Heiss *et al*[22]. Early EPCs from the old subjects were found to be significant impaired in terms of fundamental functional features like proliferation, migration and survival, although no quantitative differences in EPCs were observed. Chronic treatment with bone-marrow-derived progenitor cells from young non-atherosclerotic ApoE$^{-/-}$ mice prevents atherosclerosis progression in ApoE$^{-/-}$ mice recipients despite persistent hypercholesterolemia. In contrast, treatment with bone marrow cells derived from older ApoE$^{-/-}$ mice is much less effective[23]. Similarly, transplantation of bone-marrow-derived EPCs from young, but not old donor mice prevented a decline in the angiogenic platelet-derived growth factor signaling and cardiac angiogenesis in an aging murine model[24]. Despite these well-documented experimental studies on EPCs in aging populations, the mechanisms are still unknown and further research is needed.

EPCs AND CORONARY HEART DISEASE

In human studies, circulating EPC levels have been inves-

tigated as surrogate markers of coronary artery disease (CAD) severity and indices of clinical outcome, with significant results[25-28].

The activity and migratory capacity of EPCs is reduced in patients with coronary heart disease[29]. Furthermore it has been shown that EPCs enhance angiogenesis, promote vascular repair, improve endothelial function, inhibit atherosclerosis and increase ventricular function after myocardial infarction[5,9,30-32]. All these findings indicate that the number of EPCs may be a marker of cardiovascular risk. EPCs levels were also inversely correlated with the occurrence of in-stent restenosis[33].

EPCs AND CHRONIC HEART FAILURE

Very few research groups have studied circulating EPCs levels in chronic heart failure (CHF). Specifically, it has been shown that EPC mobilization occurs in a biphasic pattern in CHF; increased in mild stages, and depressed in advanced CHF[34,35]; possibly due to the myelosuppressive role of cytokines such as tumor necrosis factor-α in severe CHF. A significant progressive increase of EPCs was noted in patients admitted with acute exacerbation concomitantly with their clinical amelioration during hospitalization[36].

Interestingly, Geft *et al*[35] have studied early and late apoptotic progenitor cells in CHF, showing that severe heart failure patients exhibited higher numbers of late apoptotic progenitors, and there was a significant association of the latter cells with disease severity. However, in another clinical study, the authors reported that there was no correlation between $CD34^+$ circulating cells and New York Heart Association (NYHA) functional class[37].

Further research is needed to clarify the clinical significance of EPCs levels and their role in CHF patients in relation to acute exacerbations and disease severity.

EPCs AND LEFT VENTRICULAR ASSIST DEVICES

Over the past 4 years a few studies investigated the role of left ventricular assist device (LVAD) implantation in the number of EPCs in patients with end-stage CHF (NYHA class Ⅲ or Ⅳ). In a recent study, Jahanyar *et al*[38] have demonstrated that LVADs cause a significant increase of stem cell factor and its receptor (c-kit) gene expression, which coincided with a surge of mast cells after ventricular unloading. In another study[39], a significant increase in EPCs was also reported after LVAD implantation.

Both studies were limited by the small number of participants and the lack of an adequate control group. In the study of Jahanyar *et al*[38] the patients' EPCs were compared to tru-cut biopsies of donor hearts, while in the study of Manginas *et al*[39], the control group comprised patients who were ineligible for LVAD implantation.

In addition, in an experimental study[40], the research group found that the intramuscular injection of EPCs [in particular KLS cells ($Lin^-/c\text{-}kit^+/Sca1^+$)] in the LV-unloading heart of rodents, may have a protective effect against cardiac systolic dysfunction and myocardial atrophy. The latter study suggests that this intervention may have a clinical potential as a combination therapy together with LVAD implantation.

Besides the nature of the study populations with the methodological flow limiting results, it seems that LVAD implantation increases EPC levels.

EPCs AND PULMONARY ARTERIAL HYPERTENSION

Endothelial dysfunction is strongly involved in the pathophysiology of pulmonary arterial hypertension (PAH)[41]. For this reason a growing interest has been recently raised in the role of EPCs in PAH. In a study of Smadja *et al*[42], the number of circulating endothelial cells was significantly higher in 10 patients with irreversible PAH than in 16 patients with reversible PAH and five control subjects, while progenitor cells did not differ among the groups. To make things more confusing it has also been reported that a significant decrease was observed in circulating EPCs in 20 patients with idiopathic PAH compared to 20 healthy controls[43]. Accordingly, Hansmann *et al*[44] reported that EPC numbers were 50% lower in PAH subjects versus matched controls.

In contrast with previous studies mentioned above it has been reported that EPCs were increased in patients with PAH compared with controls[45]. In a recent clinical trial, where nine patients with PAH, nine patients with chronic thromboembolic pulmonary hypertension (CTEPH), and seven subjects with normal pulmonary arterial pressure were enrolled, the researchers concluded that EPCs were significantly increased in PAH patients compared to CTEPH and controls[46].

The results from the above studies appear conflicting, thus, further research is needed to clarify the role of EPCs in PAH. Research on EPCs should target on the different PAH stages, and the PAH diagnosis duration that might differentiate in terms of number and function.

EPCs AND CRITICAL ILLNESS

Recent innovative studies have shown that mobilization of EPCs occur in critically ill patients and are significantly associated with clinical outcome and prognosis[47-51].

In 2001, an increased number of EPCs in patients with sepsis and septic shock was found compared to healthy subjects[49]. These findings were confirmed in a more recent study by Rafat *et al*[47]. They reported that after studying 32 intensive care unit patients with sepsis, 15 patients without sepsis and 15 healthy controls, the number of EPCs was not only significantly higher in septic patients compared to non-septic patients and controls, but was also associated with survival. In a methodologically similar study, Burnham *et al*[48] have shown that increased number of EPCs was highly correlated with

improved survival in patients with early acute lung injury. In addition, in a prospective study enrolling 44 patients with ventilator-associated pneumonia and sepsis, the research group concluded that EPCs count on day 1 was correlated with survival[50]. These studies suggest that patients with sepsis appear to present with elevated EPCs numbers compared to healthy controls, and furthermore, that EPCs levels are strongly correlated with outcome.

EPCs AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

To the best of our knowledge, only a few studies[52-54] have investigated the number of EPCs in patients with chronic obstructive pulmonary disease (COPD). Methodological differences might have played a significant role in the fact that the studies had conflicting results. Peinado *et al*[52] conducted dissection on pulmonary arteries of lung specimens of 15 patients undergoing lung resection because of carcinoma and compared the EPC numbers in nine subjects with moderate to severe COPD to the six subjects free of COPD. The authors concluded that EPCs were significantly greater in number in COPD patients.

In contrast to that study, two other controlled studies[53,54] reported lower levels of EPCs in blood samples from COPD patients compared to controls. The number of EPCs was also strongly correlated to disease severity for both studies. In a study by Sala *et al*[55], the authors investigated the response of EPCs to episodes of exacerbation of COPD (ECOPD). After studying 35 patients hospitalized because of ECOPD, 44 COPD patients, 10 smokers free of COPD and 10 healthy non-smokers, they found a higher level of EPCs in the ECOPD group compared to the other groups. Just recently, it has been shown that there is an impaired EPC mobilization and colony-forming capacity in COPD patients with stage I and II lung cancer undergoing thoracic surgery[56]. It seems that more evidence is necessary to understand better the role of EPCs in COPD due to the inconclusive results mentioned above.

EPCs AND OBSTRUCTIVE SLEEP APNEA

Four controlled studies[57-60] have been conducted to investigate the number of EPCs in patients with obstructive sleep apnea (OSA), who lacked cardiovascular disease and were free of any other known cardiovascular risk factor. All studies had a small number of participants and reported conflicting results. El Solh *et al*[60] by studying 14 subjects with OSA documented higher numbers of EPCs compared to 10 healthy controls. They also reported that an 8-wk treatment with continuous positive airway pressure (CPAP) therapy significantly reduced the levels of EPCs in the OSA patient group. The same research group a year later confirmed the above outcome by enrolling 35 OSA patients on 8 wk nasal CPAP therapy[58].

In another study that included 13 OSA patients and 13 controls, there was a reduced number of EPCs in patients with OSA compared to controls[59]. However, other researchers found no significant differences in EPCs between OSA patients and controls[57].

The conflicting results of the above studies need further investigation with larger numbers of study participants before conclusions can be made for the possible role of EPCs in OSA. Disease severity might play a significant role in the EPCs level and should be further assessed.

EPCs AND DIABETES

In diabetic patients the EPC levels are significantly reduced compared to non-diabetic controls. Loomans and colleagues reported that the EPCs numbers were decreased in patients with type I diabetes, compared to EPCs levels in healthy subjects[61]. Enrolling 74 patients with type I diabetes, EPCs counts were significantly lower in these patients compared to 80 healthy controls[62].

Similarly, other studies have also demonstrated that EPCs levels were lower in patients with diabetes mellitus type II compared to healthy controls[63-65]. Treatment with strict glycemic control and total cholesterol improvement increased EPCs numbers[65]. There is strong evidence that patients with diabetes types I and II appear to have lower EPCs numbers compared to healthy controls. Further research is needed demonstrating the beneficial effects of the potential increase in EPCs by certain therapeutic measures (diet, exercise training, antidiabetic drug treatment, *etc*.).

EPCs AND CEREBROVASCULAR DISEASE

In a study of Ghani *et al*[66], there was a significant difference in EPC counts between stroke patients (acute stroke: median 4.75, range 0-33; stable stroke: median 7.25, range 0-43) and control subjects (median 15.5, range 4.3-50), independent of age. In contrast, Yip *et al*[67] demonstrated that the levels of circulating EPCs did not differ between patients with ischemic stroke and normal control subjects. The authors also reported that in patients with acute ischemic stroke, the EPCs levels were significantly higher than in subjects at high cerebrovascular risk, but appeared to be lower in patients with severe neurological impairment. The research group stated that the inconsistency of their findings with the results of Ghani *et al*[66] was due to the difference in the time interval for blood sampling between the studies.

There was a significant decrease in circulating $CD34^+$ cell levels in 25 patients with a history of atherothrombotic cerebral ischemic events compared with age-matched controls[68]. Colony forming units (CFUs) and outgrowth cell population as a subset of EPCs were significantly reduced in 75 patients with acute stroke, compared with 45 patients with chronic stroke and 40 age-matched control subjects. Moreover, patients with large artery atherosclerosis had much lower CFU numbers and functional activities

than the ones with cardioembolism[69].

It has also been reported that the increase in circulating EPC levels after acute ischemic stroke is associated with good functional outcome and reduced infarct growth, suggesting that EPCs might participate in neurorepair after ischemic stroke[70]. There are convincing data that ischemic stroke is strongly correlated with low EPC levels and that levels are strongly correlated with functional outcome in acute ischemic stroke.

EPCs AND PERIPHERAL ARTERIAL DISEASE

Little information is available on EPC mobilization in patients with peripheral arterial disease (PAD). In 2008, Delva *et al*[71] studied the number of EPCs by different methods in a carefully selected group of 45 patients with CAD along with 24 healthy subjects. In patients with PAD, by utilizing the dual-binding method, the number of circulating EPCs was significantly increased compared to that in healthy controls. On the contrary, while using fluorescence-activated cell sorting analysis the results were different, both $CD34^+$ and $CD133^+$ cell counts were significantly decreased compared to controls. The use of different methods in data collection may explain the discrepancy. Finally, CFUs were significantly increased in PAD compared to healthy subjects[71].

After studying 48 PAD patients and 22 patients without PAD the researchers concluded that EPC mobilization occurred in PAD and showed a biphasic response, with elevated EPC levels in the moderate phase and reduced EPC levels in the advanced phase. EPC levels were also associated with the levels of novel circulating biomarkers and several aspects of PAD, including the severity, progression and disease outcome[72].

As a result of the limited number of studies, further research is needed on the levels of EPCs in patients with PAD. It seems however, that there is an increase of EPC levels in the moderate phase and a decrease in the advance phase of PAD.

EPCs AND ARTERIAL HYPERTENSION

In the very early stage of hypertension a significant increase in circulating progenitor cells is associated with reactive oxygen species and oxidative stress[73]. Vasa *et al*[19], after studying patients with CAD concluded that the migratory capacity of EPCs was reduced in those patients with hypertension, although their total number did not change significantly.

Additionally, only recently it has been demonstrated that the *in vivo* endothelial repair capacity of early EPCs is substantially impaired in patients with newly diagnosed pre-hypertension and hypertension as their only cardiovascular risk factor[74]. Increased senescence of early EPCs in pre-hypertensive and hypertensive patients was related to abnormal EPCs endothelial repair capacity. In the same study there was not a significant difference in the numbers of EPCs and endothelial apoptotic microparticles in pre-hypertensive and hypertensive patients when compared with healthy controls. From this study emerges evidence that the endothelial repair capacity of early EPCs is substantially impaired in hypertensive patients.

EPCs AND OBESITY

It is well established that obesity is associated with decreased numbers of EPCs[75-79]. The number of circulating EPCs is lower in obese compared with overweight and normal weight subjects, while EPCs colony forming capacity is blunted in overweight and obese compared with normal weight subjects[76]. Tobler *et al*[77] also stated that reduced numbers of EPCs along with their premature senescence might contribute to the development and progression of vascular dysfunction in obesity. Furthermore, the function of EPCs in obesity is impaired either by the impaired ability of circulating EPCs to release proangiogenic growth factors compared with normal weight adults and by the lower EPC resistance to an apoptotic stimulus in overweight and obese compared to normal weight[78]. Interestingly, low EPCs levels[75] and their functional deficiency[79] can be reversed after significant weight reduction.

A summary of the above studies of EPCs in different disease populations is reported in Table 1.

PHYSICAL ACTIVITY, EXERCISE TRAINING AND ENDOTHELIAL FUNCTION

It is well recognised that physical activity has significant beneficial effects on overall health, and especially on cardiovascular morbidity and mortality. Physical inactivity is an independent risk factor for the development of coronary heart disease, stroke and peripheral vascular disease[80].

Regular physical activity significantly attenuates the atherosclerotic process by reducing atherosclerotic risk factors, retarding arterial wall aging[81,82], delaying development of endothelial dysfunction and preserving vascular function[83]. Furthermore, physical training reduces vascular oxidative stress, increases the activity of endothelial nitric oxide synthase (eNOS)[84] and results in increased blood flow to oxidative skeletal muscle fibers[85].

Accordingly, the beneficial effects of exercise have been reported in patients with CAD as part of the secondary prevention[86,87]. It is well known that physical training improves endothelial function and exercise capacity in patients with CAD[88], CHF[89] and PAD[90]. Exercise is also associated with improved body weight, blood pressure, insulin sensitivity and hemostatic and inflammatory variables[91,92]. High-intensity interval training is a relative novel alternative modality of exercise in metabolic syndrome[93], coronary heart disease[94] and in CHF patients[95-97], allowing more intense stimuli in the peripheral muscles. The addition of strength training has been also shown to confer significant improvement in endothelial function[98,99] and peripheral microcirculation[100] in CHF patients.

Table 1 Summary of endothelial progenitor cell levels in different disease populations

Disease	Results	Comments	Ref.
Aging	↓ EPCs proliferation ↓ EPCs migration ↓ EPCs survival		[20,22]
Coronary heart disease	↓ EPC activity ↓ EPC migratory capacity		[29]
CHF	↑ EPC levels in mild stages[34,35] ↑ EPC levels in acute exacerbation[36] ↑ Late apoptotic progenitors[35] ↓ EPC levels in advanced stages[34,35]		[34-36]
LVADs	↑ EPC levels		[38,39]
PAH	↑ EPC levels[42,45,46] ↓ EPC levels[43,44]	Conflicting results	[42-46]
Critical illness	↑ EPC levels in sepsis and septic shock[47,49] ↑ EPC levels in early acute lung injury[48]		[47-49]
COPD	↑ EPC levels[52] ↓ EPC levels[53,54] ↑ EPC levels in exacerbation of COPD[55] ↓ EPC mobilization and colony-forming capacity[56]	Conflicting results	[52-56]
OSA	↑ EPC levels[58,60] ↓ EPC levels[59] - No difference[57]	Conflicting results	[57-60]
Diabetes mellitus type I and Ⅱ	↓ EPC levels		[61-65]
Cerebrovascular disease	↓ EPC levels in stroke[66] - No difference in ischemic stroke[67] ↑ EPC levels in acute ischemic stroke[67] ↓ EPC levels in atherothrombotic cerebral ischemic event[68] ↓ EPC colony forming in acute stroke[69]		[66-69]
PAD	↑ EPC levels in moderate phase ↑ EPC levels in advance phase		[71,72]
Arterial hypertension	↑ EPC levels in early stage of hypertension[73] ↓ EPC migratory capacity in CAD and hypertension[19] - No difference on EPC levels in pre-hypertensive and hypertensive[74]		[19,73,74]
Obesity	↓ EPC levels[75-77] ↓ EPC colony forming capacity[76]		[75-79]

EPC: Endothelial progenitor cell; CHF: Chronic heart failure; LVAD: Left ventricular assist device; PAH: Pulmonary arterial hypertension; COPD: Chronic obstructive pulmonary disease; OSA: Obstructive sleep apnea; PAD: Peripheral arterial disease; CAD: Coronary artery disease.

It has become common knowledge that exercise training has a significant therapeutic role in a vast majority of diseases. A structured exercise training program, and more specifically a combination of aerobic exercise (continuous or high-intensity interval training) with or without the addition of strength training can significantly attenuate the atherosclerotic process through its beneficial effects on endothelial function[93,95,98-100]. However, there is growing interest concerning the role of exercise training on EPCs that may interact with endothelium function; this issue is currently under investigation from several research groups in both healthy subjects and diseases.

EFFECTS OF EXERCISE TRAINING ON EPCs

Laufs *et al*[101] in 2004 were the first research group to demonstrate that physical activity leads to an increased number of circulating EPCs in mice after 28 wk of running wheels. This effect occurred rapidly (7 d after training) and was sustained for at least 4 wk, providing evidence that EPC numbers can be increased by nearly threefold by exercise training. These findings were confirmed by another research group in a human study in which middle aged and older subjects following a 3 mo training program of walking, at moderate intensity, increased circulating angiogenic cell (CAC) migratory capacity by 50%[20]. Accordingly, Yang *et al*[102] showed that the number and activity of circulating EPCs of 10 older and 10 young sedentary healthy men were increased after 3 mo regular exercise. However, the increased number and activity of circulating EPCs of older sedentary healthy men was higher compared to the younger group. In contrast, in a study of 20 healthy men who followed a 6-wk interval exercise training program, [moderate (9 subjects) or high intensity (11 subjects)], there was no significant effect on EPC number in both groups, even though there was an improvement of vasoconstrictor function[103].

Furthermore, a study of 182 children (aged 11.1 ± 0.7 years) showed that physical activity by means of daily school exercise lessons can increase the number of circulating progenitor cells[104]. More interestingly, EPC numbers decreased significantly after 10 d of detraining in highly active older men, even lower than the level of low-active (sedentary) men[105]. These findings agree with the fact that sustained physical activity is necessary to preserve improved endothelial function for maintaining long-term training effects[106].

In an animal study, 8 wk of aerobic training in mice with advanced atherosclerotic lesions showed no improvement in atherosclerosis, whereas mice with early lesions benefited. The authors suggest that the impact of exercise on atherogenesis is primarily to retard the progression to advanced lesions, rather than reversing advanced lesions. Interestingly, the level of EPCs decreased, along with proinflammatory cytokines in response to exercise[107].

In another experimental study conducted in the early phase following traumatic brain injury in rats, the exercise group compared to the control group enhanced significantly proliferation of neural stem cells (NSCs) around the damaged area[108].

Despite the significant experimental study of Laufs *et al*[101], Luk *et al*[109] showed that there was no significant increase in CD34/KDR$^+$ EPCs after an 8-wk exercise training programme on 32 patients with CAD compared to controls. In contrast, in a recent uncontrolled study by

Cesari *et al*[110], there was a significant increase in EPCs and a significant decrease in proinflammatory biomarkers, in patients with acute coronary syndrome, occurring after a 30-d period of cardiac rehabilitation (3 sessions per week of endurance training on a cycle ergometer, at 60%-70% of individual VO_2 level obtained at peak exercise during baseline symptom-limited cardiopulmonary exercise testing). Because of the conflicting results and the small number of studies, more human studies are needed to clarify the possible beneficial effects of exercise on EPCs in CAD.

EPC levels [assessed as $CD34^+$ cells coexpressing AC133 and vascular endothelial growth factor receptor 2 (VEGFR2), and as endothelial CFUs (e-CFUs)] were also evaluated in chronic renal failure patients on hemodialysis after a 6-mo walking exercise program. This study showed that there was not a significant change in $CD34^+$ or $CD34^+/AC133^+/VEGFR2^+$ cell numbers, but there was a significant change in e-CFUs[111].

A significant enhancement of circulating EPCs after 8 wk of supervised exercise training has also been demonstrated in CHF patients. In that study, 8 wk of detraining led to baseline EPC levels[112]. In a recent study by Van Craenenbroeck *et al*[113] similar results have emerged after investigating the effect of 6 mo exercise training in CHF, compared with a no exercise CHF group and a no exercise group of healthy subjects. The authors reported a reverse effect of exercise training on circulating angiogenic cell dysfunction and an increase in EPCs. An analogous increase in EPC numbers was found, after short-term exercise training (3 wk) in 14 CHF patients[114]. The exercise program was a combination of calisthenics and aerobic exercise with an intensity up to 75%-85% of the maximum heart rate attained in the exercise test. The authors reported that even a relatively short-term exercise training program significantly improved the serum ability to support viability of EPCs as well as upregulation of proteins participating in LV remodeling.

Similarly, 37 CHF patients (LV ejection fraction 24% ± 2%) were randomly assigned to 12 wk of exercise training (n = 18) or sedentary lifestyle (n = 19). Exercise training increased the number of $CD34^+$ progenitor cells from 1094 ± 677 to 1450 ± 798 cells/mL blood in the training group (P = 0.032 *vs* control). The number of $CD34^+/KDR^+$ EPCs was found to be augmented from 100 ± 127 to 183 ± 156 cells (P = 0.014 *vs* control) and their migratory capacity by 224 ± 263 *vs* -12 ± 159 CPCs/1000 plated CPCs in controls (P = 0.03)[115].

The most recent paper on the effect of exercise training in patients with CHF is the one published by Mezzani *et al*[116]. Patients (n = 30) with NYHA class Ⅱ were allocated to either an aerobic 3-mo exercise training group or a control group, while seven age-matched healthy subjects were also studied. In addition to the previous studies, the authors reported that the numbers of EPCs, even though they did not differ between patient groups at baseline, significantly increased in the CHF training group, reaching values similar to those of healthy controls, while the difference between CHF controls and healthy controls did not reach statistical significance. Additionally, the levels of EPCs remained unchanged in the control patient group.

In a randomized controlled clinical trial, 40 patients with PAD were allocated to either an exercise or a control group. The intervention group followed a standardized training program twice a week for 6 mo. The initial duration included 35 min of intermittent walking, which was increased by 5 min each session until 50 min of intermittent walking was achieved. EPC levels were significantly increased and asymmetric dimethylarginine levels were decreased in the exercise group compared with the controls. The authors suggested an enhanced angiogenesis and improved endothelial function that might contribute to cardiovascular risk reduction[117].

The first study on the effect of exercise training in overweight and obese patients has recently been published by Cesari *et al*[118]. Even though the study had a few methodological limitations, the authors reported a significant increase in all the three groups of EPCs ($CD34^+/KDR^+$: +33.3%; $CD133/KDR^+$: +35%; $CD34^+/CD133^+/KDR^+$: +35.7%) after a 3 mo exercise intervention program, compared to baseline measurements.

The underlying mechanisms of the effect of exercise training on EPC levels needs further investigation, but taken together with the existing data, it has been suggested that physical exercise increases NO bioavailability[119], and in parallel with this fact, the effect of physical activity on EPCs is markedly reduced after inhibition or deletion of eNOS, which suggests an NO-dependent increase in EPCs in response to exercise[101,113]. Additionally, it has been reported that physical exercise may increase EPC numbers by prolonging their lifespan. Data derived from cultured EPCs have indicated that the observed EPCs enhancement in the circulation and the bone marrow could be explained partly by antiapoptotic effects of physical activity on EPCs and potentially their progeny[101]. The extra muscle stress that is additive to hypoxic stress and leads to a hypoxia-induced factor-1-mediated upregulation of both VEGF and stromal-cell-derived factor (SDF)-1 stimulated EPCs mobilization, as demonstrated by Sarto *et al*[112].

Even though the studies mentioned above followed different methodologies and exercise training protocols, we may assume that regular exercise training increases significantly circulating EPC levels, both in healthy subjects (rodents and humans) and in a variety of diseases. The strongest evidence so far in cardiovascular disease emerges from studies in CHF and PAD. More data are needed, however, to confirm the results of these preliminary studies and to investigate the optimum exercise protocol in order to maximize the possible beneficial effects.

Summaries of the long-term exercise training effects on EPCs in animals and healthy subjects as well in disease populations are illustrated in Tables 2 and 3, respectively.

EFFECT OF ACUTE EXERCISE ON EPCs

The effect of a single exercise session on EPC levels has also been investigated. Rehman *et al*[120] have demon-

Table 2 Effects of exercise training on endothelial progenitor cells in animals and healthy subjects

Subjects	*n*	Study group; age	Modality	Exercise prescription	Duration	Results	Limitations	Ref.
Mice	12	Exercise group; Control group	Aerobic	Exercise group: Voluntary running 5100 ± 800 m 7 d a week; Control group: No intervention	28 d	↑ EPCs		[101]
Healthy male	10	Exercise (n = 10) 59 ± 2 yr	Home based aerobic	Walking/jogging 60%-75% predicted peak HR 40-50 min-5-7 sessions per week	3 mo	↑ EPC colonies about 100% from 10 ± 3 to 22 ± 5; ↑ Migratory activity about 50% from 683 ± 96 to 1022 ± 123 RFUs	Non control study	[20]
Healthy male	47	Exercise: Elderly (n = 25) 67.8 ± 3.38 yr, young (n = 22) 26.3 ± 3.15 yr	Aerobic	Treadmill 30 min 3 sessions per week	12 wk	↑Re-endothelialization capacity of EPCs from 15% ± 4% to 36% ± 9%	Non control study	[102]
Healthy male (n = 7), female (n = 13)	20	Interval exercise: Moderate (n = 9), heavy (n = 11)	Aerobic	Ergometer moderate interval (10 s @ 120% peak work rate : 20 s @ 20 W); Heavy interval (30 s @ 120% peak work rate : 60 s @ 20 W), 30-40 min 3 sessions per week	6 wk	No significant change on EPC numbers	Non control study measurements took place 48 h after the last session	[103]
Children	182	Intervention (n = 109), control (n = 73)		Intervention group: PA at school 45 min + endurance training 15 min per school day; Control group: PA at school 45 min 2 school day per week	1 school year	↑ CPCs		[104]

EPC: Endothelial progenitor cell; PA: Physical activity.

strated that exercise can acutely (within 5-10 min after completion of exercise) increase EPCs and CACs in 22 volunteer patients that underwent a symptom-limited treadmill or bicycle exercise test. It has been reported that a modified Bruce treadmill acute exercise protocol can significantly contribute to upregulation of circulating EPCs in healthy subjects[121]. In the same study, the plasma NO levels were also increased and there was a significant linear relationship between the enhanced plasma NO levels and increased number of circulating EPCs activity after acute exercise.

Since that study, researchers have sought to investigate the effect of a single bout of strenuous exercise on late outgrowth endothelial cells (OECs). In a non-controlled study of 11 healthy, physically fit subjects, who followed 1 h of high-intensity (80% of the predicted maximum heart rate) aerobic exercise, the numbers of OEC colonies were doubled 1 h after exercise compared to baseline measurements. The OEC levels returned back to baseline levels 48 h after exercise[122]. In another study[123], it was shown that strenuous exercise at 70% of the individual anaerobic threshold for 4 h could lead to a significant rise in progenitor cells (hematopoietic and EPCs).

In a recent study[124], exercise-induced changes in putative EPC gene expression were associated with thrombin production and the authors suggested that they may be increased by long-term exercise training. Moreover, in a study by Van Craenenbroeck *et al*[125], the authors analyzed the concentration of EPC levels before and immediately after a maximal cardiopulmonary exercise test, showing a significant increase of 50% in EPCs.

The acute effect of different exercise durations and intensities on EPC levels was also studied in healthy individuals[126]. In that study, the authors reported that intensive and moderate aerobic exercise for 30 min but not for 10 min increased circulating levels of EPCs.

Furthermore, the analysis of EPC levels in 68 healthy marathon runners after finishing a marathon race, demonstrated no change compared to baseline levels[127]. Similarly, in a more recent study[128], EPC levels were measured in a group of 10 healthy amateur runners after finishing a marathon and after completing a 1.5-km field test. The researchers observed no change in EPC levels after the marathon, while there was a significant increase after the field test. In addition, Goussetis *et al*[129] showed a significant increase in inflammatory markers, which correlated with a rise in EPCs levels in amateur spartathlon runners (246 km). An interesting finding of this study was also the observation that endothelial cell colonies derived from mobilized EPCs contained significantly more cells 48 h after the race than those obtained in controls and in athletes before the race.

While studying a group of healthy young subjects, a group of healthy old and a group of patients with PAD after an acute exercise session, Shaffer *et al*[130] concluded that young healthy individuals have an increased capacity to mobilize EPCs, as compared with older individuals. Interestingly, patients with PAD appeared to be unable to mount a significant increase in circulating EPCs, despite the ischemic stimulus. Van Craenenbroeck *et al*[131] studied 41 CHF patients (22 mild, 19 severe) and 13 healthy subjects while performing a symptom limited cardiopulmonary exercise test. Even though there was no significant change in circulating $CD34^+$ cells and $CD34^+/KDR^+$

Table 3 Effects of exercise training on endothelial progenitor cells in different disease populations

Subjects	*n*	Study group; age	Disease	Modality	Exercise prescription	Duration	Results	Limitations	Ref.
Mice	12	Exercise; Control	Advanced atherosclerotic lesions; Early atherosclerotic lesions	Aerobic	Voluntary running	8 wk	No change on advanced atherosclerotic lesions; ↑ EPC levels on early atherosclerotic lesions		[107]
Mice	10	Exercise; Control	After traumatic brain injury	Aerobic	Exercise group: Treadmill 22 m/min 30 min 7 d per week; Control group: No intervention	1 wk	↑ Neuronal stem cell		[108]
Male (n = 24); Female (n = 51)	64	Exercise (n = 32); Control (n = 32) 67.1 ± 8.4 yr old	Coronary artery disease	Aerobic + resistance exercise	Exercise group: Bicycle ergometer, treadmill, rowing, steps, arm ergometer + dumbbell, weight training 80% of HRmax 50 min + (5 min warm-up and 5 min cool down) 3 sessions per week	8 wk	No change		[109]
Male (n = 92); Female (n = 20)	112	Exercise (n = 112) 58.2 ± 9.5 yr old	After acute coronary syndrome	Aerobic	Exercise group: Bicycle ergometer 60%-70% of peak VO2 30 min + (5 min warm-up and 5 min cool down) 3 sessions per week	30 d	↑ EPC levels + ↓ pro-inflammatory markers	No controls; No homogeneity of population	[110]
Male (n = 20); Female (n = 10)	30	Exercise (n = 16); Control (n = 14) 67 ± 12 yr old	Hemodialysis	Aerobic	Exercise group: Treadmill/walking 50% max speed 10 min 2 sessions per day; Control group: No intervention	6 mo	No change	Small sample size; No standarized work	[111]
Male (n = 16); Female (n = 6)	22	Exercise (n = 22) 61.4 yr old (SE 1.60)	CHF NYHA Ⅱ or Ⅲ	Aerobic	Exercise group: Bicycle ergometer 60% of HR reserve 45 min + (5 min warm-up and 5 min cool down) 3 sessions per week	8 wk	↑ EPC levels	No controls; No homogeneity of population	[112]
Male (n = 30); Female (n = 8)	38	Exercise (n = 21) 61.3 ± 2.2 yr old; Control (n = 17) 63.4 ± 3 yr old	CHF	Aerobic	Exercise group: 90% HR 60 min 3 sessions per week; Control group: No intervention	6 mo	Improves CAC migratory capacity; ↑ EPC levels	No randomization	[113]
Male (n = 16); Female (n = 12)	28	Exercise (n = 14) 72 ± 11 yr old; Control (n = 14) 73 ± 11 yr old	CHF Exercise NYHA Ⅱ; Control NYHA Ⅰ	Calistenics + aerobic	Exercise group: Bicycle ergometer 75%-85% of HRmax 30 min 2 sessions per day 6 sessions per week; Control group: No intervention	3 wk	↑ EPC levels	Small sample size	[114]
Male	37	Exercise (n = 18) 60 ± 11 yr old; Control (n = 19) 62 ± 10 yr old	NYHA functional class Ⅲb	Aerobic + calisthenics + noncompetitive ball games	Exercise group: Bicycle ergometer in hospital (50% of VO2max 5-20 min, 3-6 sessions per day, 3 wk) home exercise (60% of VO2max 20-30 min, 7 sessions per week, 12 wk) + 1 supervised session (60 min, walking, calisthenics, ball games); Control group: No intervention	12 wk	↑ EPC levels		[115]
Male	37	Exercise (n = 15) 65 ± 7 yr old; CHF control (n = 15) 63 ± 7 yr old; Healthy control (n = 7) 66 ± 4 yr old	NYHA functional class Ⅱ	Aerobic	Exercise group: Bicycle ergometer HR of ventilatory threshold 30 min 5 sessions per week; Control groups: No intervention	3 mo	Exercise group ↑ EPC levels; Control patient group no change		[116]
Male (n = 24); Female (n = 16)	40	Exercise (n = 30) 69 ± 8 yr old; Control (n = 20) 70 ± 11 yr old	PAD	Aerobic	Exercise group: Treadmill intermittent walking 5-10 min warm-up 35-50 min 2 sessions per week; Control group: No exercise intervention	6 mo	↑ EPC levels		[117]
Male (n = 22); Female (n = 18), median age 48 yr	40	Exercise (n = 40); Group A (n = 21) compliant individuals; Group B (n = 19) noncompliant individuals	Overweight and obese BMI ⩾ 25 kg/m²	Aerobic	Non supervised self reported walking briskly or moderate running 45 min HR @ the individual anaerobic threshold 3 sessions per week	3 mo	Group A ↑ EPC levels; Group B no change	Small sample size; Limited duration of follow-up; Non valid compliance measurement; Unable to distinguish which (exercise or weight change) contributed to the increased EPC levels	[118]

EPC: Endothelial progenitor cell; BMI: Body mass index; NYHA: New York Heart Association; CHF: Chronic heart failure; CAC: Circulating angiogenic cell; PAD: Peripheral arterial disease.

Table 4 Acute effects of exercise in healthy subjects

Subjects	*n*	Study group; age (yr)	Modality	Exercise	Results	Limitations	Ref.
Men	22	Healthy 54 ± 10	Symptom limited exercise test	Treadmill/bicycle	↑ EPC + ↑ CAC		[120]
Men	16	Healthy 25.1 ± 2.7	Bruce modified	Treadmill	↑ EPC + ↑ NO level		[121]
Men (*n* = 2); Women (*n* = 9)	11	Healthy 31 ± 16	1 h Spinning session	Bicycle 80% HRmax	↑ OEC	No accurate peak VO2 measurements, no gender differentiation	[122]
Men	18	Healthy (sportive) 32.4 ± 2.3	Ergometer test	Bicycle 70% IAT 240 min	↑ EPC	No control	[123]
Men	23	Endurance athletes 62 ± 1.6; Healthy low active 65 ± 1.5	Exercise test	Treadmill 75% ± 5% VO2max 30 min (5 min ramp-up + 25 min + 3 min cool down)	No change in both groups, no change between groups		[124]
Men; Women	25	Group Ⅰ (*n* = 11) 23.9 ± 1.4; Group Ⅱ (*n* = 14) 36.2 ± 9.3	Symptom limited cardiopulmonary exercise test	Bicycle ergometer: 40 W warm up; 20 W incremental test	↑ EPC	Small sample size	[125]
Men	25	Healthy	Running exercise	Protocol 1 30 min 100% IAT; Protocol 2 30 min 80% IAT; Protocol 3 10 min 80% IAT	Protocol 1 ↑ EPC; Protocol 2 ↑ EPC; Protocol 3 no change		[126]
Men	68	Marathon runners 57 ± 6	Marathon	Race	No change		[127]
Men	10	Marathon protocol (*n* = 9) 43.6 ± 11.6; Field test protocol (*n* = 8) 43.4 ± 10.9	Running exercise	Marathon protocol marathon race; Field test protocol 1500 m max speed	Marathon protocol no change; Field test protocol ↑ EPC		[128]
Men	20	Spartathlon runners (*n* = 10) 42.8 ± 1.4 Control sedentary (*n* = 10) 42.2 ± 10.4	Spartathlon	Exercise group race (246 km); Control group no intervention	Spartathlon runners ↑ EPC; Control no change		[129]

EPC: Endothelial progenitor cell; CAC: Circulating angiogenic cell; IAT: Individual anaerobic threshold.

progenitor cells, an improvement in CAC migratory capacity was most prominent in severe CHF, increased to levels that were no longer different from healthy controls. The same research group just recently sought to investigate whether the above result reflected an attenuated or delayed mobilization of EPCs, so they measured $CD34^+$/KDR^+ EPCs over a longer time period post-graded exercise testing (GXT). Even though the number of subjects was small (7 CHF patients and 8 healthy controls), the authors reported that EPC numbers increased within 10 min following GXT and remained elevated for up to 2 h. In CHF patients, the initial increase was small and normalized within 30 min[132].

From the current literature it emerges that the acute effect of a single exercise session, either performed as an exercise test, or as a single bout of strenuous exercise, can lead to a significant rise in EPCs in healthy subjects. On the contrary, there are still conflicting data with regard to long distance runners (e.g., marathon, spartathlon) and for this reason further investigation is required prior to definite conclusions. In CHF patients it seems that acute exercise might exert a rise in EPCs; however, the small number of studies with different exercise protocols, methodologies and the small number of study participants limit preliminary study results. Further investigational studies targeting on exercise characteristics (modality of exercise, intensity, duration, *etc.*) are also needed to elucidate the acute exercise effects on EPCs in CHF.

Schematic results from the acute effects of exercise in healthy subjects and disease are presented in Tables 4 and 5.

The mechanisms behind the exercise-induced mobilization of EPCs are not fully understood. In patients with cardiovascular disease, exercise-induced ischemia seems to stimulate augmentation of EPCs[133]. In healthy subjects, tissue ischemia is not normally expected to occur due to exercise, but strenuous exercise at levels above what is defined as anaerobic levels, might induce oxidative stress and an inflammatory response and thus could stimulate the release of EPCs from the bone marrow[121,122]. Researchers have hypothesized[34,132] that, in an attempt to address vascular damage, EPCs show a compensatory increase in patients with mild to moderate CHF. Interestingly, VEGF and SDF are potent angiogenic factors that have been shown to increase after exercise sessions with concomitant rise in EPCs in cardiovascular disease, indicating a possible pathophysiological link. Therefore, endothelial factors, cytokines, bone-marrow-derived factors and oxidative stress are involved throughout exercise training and may explain exercise beneficial effects in health and cardiovascular disease.

In conclusion, recent studies provide evidence for the novel concept that physical activity, either performed as a single exercise session or performed as part of an exercise training program, results in a significant increase in circulating EPC levels. Moreover, in patients with cardiovascular disease, exercise training markedly improves vascular endothelium. However, future studies with larger sample sizes are required to investigate and confirm possible exercise training-induced EPCs rise in both healthy subjects and specific subsets, such as patients with hypertension, obesity, OSA, dyslipidemia, diabetes, CAD, PAD, or CHF. Studies should aim to characterize the optimum

Table 5 Acute effects of exercise in different disease populations

Subjects	*n*	Study group; age (yr)	Disease	Modality	Exercise prescription	Duration	Results	Ref.
Men	37	Young group (n = 9), mean age 33; Old group (n = 13), mean age 66; PAD group (n = 15), mean age 69	PAD	Treadmill	Young group bruce protocol; Old group gardner protocol; PAD group gardner protocol	Young group until exhaustion or 15 min; Old group 10 min; PAD group symptom limited or 10 min	Young group ↑ EPCs; Old group no change; PAD group no change	[130]
Male (n = 41); Female (n = 13)	54	Healthy controls (n = 13) 55.7 ± 1.6; Mild CHF (n = 22) 61.9 ± 2.5; Severe CHF (n = 19) 63 ± 2.6	CHF	Bicycle ergometer	Cardiopulmonary exercise testing individualized ramp protocol	8-10 min	EPC no change; Improved CAC migration in mild CHF + severe CHF	[131]
Male (n = 13); Female (n = 2)	15	Young group (n = 4) mean age 33; Old group (n = 4) mean age 66; CHF group (n = 7) mean age 69	CHF Ⅱ / Ⅲ	Bicycle ergometer	Symptom-limited graded exercise test		↑EPCs in young group; ↑EPCs in old group; Non significant ↑EPCs in CHF group	[132]

EPC: Endothelial progenitor cell; CHF: Chronic heart failure; CAC: Circulating angiogenic cell; PAD: Peripheral arterial disease.

exercise regimen with regard to type, intensity and duration of exercise that may increase EPC levels. Confirming evidence will give the opportunity to the medical community to use a non-pharmacologic intervention, such as exercise, to mobilize EPCs. Revealing the mechanisms of exercise-induced EPC mobilization may result in the development of optimum exercise protocols to improve endothelial function and enhance angiogenesis.

REFERENCES

1 **Carmeliet P**. Mechanisms of angiogenesis and arteriogenesis. *Nat Med* 2000; **6**: 389-395
2 **Risau W**. Mechanisms of angiogenesis. *Nature* 1997; **386**: 671-674
3 **Risau W**, Flamme I. Vasculogenesis. *Annu Rev Cell Dev Biol* 1995; **11**: 73-91
4 **Asahara T**, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, Witzenbichler B, Schatteman G, Isner JM. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 1997; **275**: 964-967
5 **Hill JM**, Zalos G, Halcox JP, Schenke WH, Waclawiw MA, Quyyumi AA, Finkel T. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med* 2003; **348**: 593-600
6 **Zhang Y**, Ingram DA, Murphy MP, Saadatzadeh MR, Mead LE, Prater DN, Rehman J. Release of proinflammatory mediators and expression of proinflammatory adhesion molecules by endothelial progenitor cells. *Am J Physiol Heart Circ Physiol* 2009; **296**: H1675-H1682
7 **Takahashi T**, Kalka C, Masuda H, Chen D, Silver M, Kearney M, Magner M, Isner JM, Asahara T. Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. *Nat Med* 1999; **5**: 434-438
8 **Rosenzweig A**. Endothelial progenitor cells. *N Engl J Med* 2003; **348**: 581-582
9 **Werner N**, Junk S, Laufs U, Link A, Walenta K, Bohm M, Nickenig G. Intravenous transfusion of endothelial progenitor cells reduces neointima formation after vascular injury. *Circ Res* 2003; **93**: e17-e24
10 **Tepper OM**, Capla JM, Galiano RD, Ceradini DJ, Callaghan MJ, Kleinman ME, Gurtner GC. Adult vasculogenesis occurs through in situ recruitment, proliferation, and tubulization of circulating bone marrow-derived cells. *Blood* 2005; **105**: 1068-1077
11 **Schächinger V**, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000; **101**: 1899-1906
12 **Lerman A**, Zeiher AM. Endothelial function: cardiac events. *Circulation* 2005; **111**: 363-368
13 **Urbich C**, Dimmeler S. Endothelial progenitor cells: characterization and role in vascular biology. *Circ Res* 2004; **95**: 343-353
14 **Schmidt-Lucke C**, Rössig L, Fichtlscherer S, Vasa M, Britten M, Kämper U, Dimmeler S, Zeiher AM. Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events: proof of concept for the clinical importance of endogenous vascular repair. *Circulation* 2005; **111**: 2981-2987
15 **Moreno PR**, Sanz J, Fuster V. Promoting mechanisms of vascular health: circulating progenitor cells, angiogenesis, and reverse cholesterol transport. *J Am Coll Cardiol* 2009; **53**: 2315-2323
16 **Pacilli A**, Faggioli G, Stella A, Pasquinelli G. An update on therapeutic angiogenesis for peripheral vascular disease. *Ann Vasc Surg* 2010; **24**: 258-268
17 **Tongers J**, Roncalli JG, Losordo DW. Role of endothelial progenitor cells during ischemia-induced vasculogenesis and collateral formation. *Microvasc Res* 2010; **79**: 200-206
18 **Crosby JR**, Kaminski WE, Schatteman G, Martin PJ, Raines EW, Seifert RA, Bowen-Pope DF. Endothelial cells of hematopoietic origin make a significant contribution to adult blood vessel formation. *Circ Res* 2000; **87**: 728-730
19 **Vasa M**, Fichtlscherer S, Aicher A, Adler K, Urbich C, Martin H, Zeiher AM, Dimmeler S. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ Res* 2001; **89**: E1-E7
20 **Hoetzer GL**, Van Guilder GP, Irmiger HM, Keith RS, Stauffer BL, DeSouza CA. Aging, exercise, and endothelial progenitor cell clonogenic and migratory capacity in men. *J Appl Physiol* 2007; **102**: 847-852
21 **Kushner EJ**, MacEneaney OJ, Weil BR, Greiner JJ, Stauffer BL, DeSouza CA. Aging is associated with a proapoptotic endothelial progenitor cell phenotype. *J Vasc Res* 2011; **48**: 408-414
22 **Heiss C**, Keymel S, Niesler U, Ziemann J, Kelm M, Kalka C.

Impaired progenitor cell activity in age-related endothelial dysfunction. *J Am Coll Cardiol* 2005; **45**: 1441-1448
23 **Rauscher FM**, Goldschmidt-Clermont PJ, Davis BH, Wang T, Gregg D, Ramaswami P, Pippen AM, Annex BH, Dong C, Taylor DA. Aging, progenitor cell exhaustion, and atherosclerosis. *Circulation* 2003; **108**: 457-463
24 **Edelberg JM**, Tang L, Hattori K, Lyden D, Rafii S. Young adult bone marrow-derived endothelial precursor cells restore aging-impaired cardiac angiogenic function. *Circ Res* 2002; **90**: E89-E93
25 **Jujo K**, Ii M, Losordo DW. Endothelial progenitor cells in neovascularization of infarcted myocardium. *J Mol Cell Cardiol* 2008; **45**: 530-544
26 **Sekiguchi H**, Ii M, Losordo DW. The relative potency and safety of endothelial progenitor cells and unselected mononuclear cells for recovery from myocardial infarction and ischemia. *J Cell Physiol* 2009; **219**: 235-242
27 **Werner N**, Kosiol S, Schiegl T, Ahlers P, Walenta K, Link A, Böhm M, Nickenig G. Circulating endothelial progenitor cells and cardiovascular outcomes. *N Engl J Med* 2005; **353**: 999-1007
28 **Zeoli A**, Dentelli P, Brizzi MF. Endothelial progenitor cells and their potential clinical implication in cardiovascular disorders. *J Endocrinol Invest* 2009; **32**: 370-382
29 **Heeschen C**, Lehmann R, Honold J, Assmus B, Aicher A, Walter DH, Martin H, Zeiher AM, Dimmeler S. Profoundly reduced neovascularization capacity of bone marrow mononuclear cells derived from patients with chronic ischemic heart disease. *Circulation* 2004; **109**: 1615-1622
30 **Orlic D**, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, Pickel J, McKay R, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Bone marrow cells regenerate infarcted myocardium. *Nature* 2001; **410**: 701-705
31 **Assmus B**, Schächinger V, Teupe C, Britten M, Lehmann R, Döbert N, Grünwald F, Aicher A, Urbich C, Martin H, Hoelzer D, Dimmeler S, Zeiher AM. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation* 2002; **106**: 3009-3017
32 **Dimmeler S**, Aicher A, Vasa M, Mildner-Rihm C, Adler K, Tiemann M, Rütten H, Fichtlscherer S, Martin H, Zeiher AM. HMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway. *J Clin Invest* 2001; **108**: 391-397
33 **George J**, Herz I, Goldstein E, Abashidze S, Deutch V, Finkelstein A, Michowitz Y, Miller H, Keren G. Number and adhesive properties of circulating endothelial progenitor cells in patients with in-stent restenosis. *Arterioscler Thromb Vasc Biol* 2003; **23**: e57-e60
34 **Valgimigli M**, Rigolin GM, Fucili A, Porta MD, Soukhomovskaia O, Malagutti P, Bugli AM, Bragotti LZ, Francolini G, Mauro E, Castoldi G, Ferrari R. CD34+ and endothelial progenitor cells in patients with various degrees of congestive heart failure. *Circulation* 2004; **110**: 1209-1212
35 **Geft D**, Schwartzenberg S, Rogowsky O, Finkelstein A, Ablin J, Maysel-Auslender S, Wexler D, Keren G, George J. Circulating apoptotic progenitor cells in patients with congestive heart failure. *PLoS One* 2008; **3**: e3238
36 **Nonaka-Sarukawa M**, Yamamoto K, Aoki H, Nishimura Y, Tomizawa H, Ichida M, Eizawa T, Muroi K, Ikeda U, Shimada K. Circulating endothelial progenitor cells in congestive heart failure. *Int J Cardiol* 2007; **119**: 344-348
37 **Carvalho VO**, Ruiz MA, Bocchi EA, Carvalho VO, Guimarães GV. Correlation between CD34+ and exercise capacity, functional class, quality of life and norepinephrine in heart failure patients. *Cardiol J* 2009; **16**: 426-431
38 **Jahanyar J**, Youker KA, Torre-Amione G, Koerner MM, Bruckner B, Noon GP, Loebe M. Increased expression of stem cell factor and its receptor after left ventricular assist device support: a potential novel target for therapeutic interventions in heart failure. *J Heart Lung Transplant* 2008; **27**: 701-709
39 **Manginas A**, Tsiavou A, Sfyrakis P, Giamouzis G, Tsourelis L, Leontiadis E, Degiannis D, Cokkinos DV, Alivizatos PA. Increased number of circulating progenitor cells after implantation of ventricular assist devices. *J Heart Lung Transplant* 2009; **28**: 710-717
40 **Koike M**, Kojima H, Fujimiya M, Matsubayashi K, Aimi Y, Kimura H, Asai T. Transfer of bone marrow progenitors prevents coronary insufficiency and systolic dysfunction in the mechanical unloaded heart in mice. *J Surg Res* 2011; **171**: 47-57
41 **Tuder RM**, Cool CD, Yeager M, Taraseviciene-Stewart L, Bull TM, Voelkel NF. The pathobiology of pulmonary hypertension. Endothelium. *Clin Chest Med* 2001; **22**: 405-418
42 **Smadja DM**, Gaussem P, Mauge L, Israël-Biet D, Dignat-George F, Peyrard S, Agnoletti G, Vouhé PR, Bonnet D, Lévy M. Circulating endothelial cells: a new candidate biomarker of irreversible pulmonary hypertension secondary to congenital heart disease. *Circulation* 2009; **119**: 374-381
43 **Junhui Z**, Xingxiang W, Guosheng F, Yunpeng S, Furong Z, Junzhu C. Reduced number and activity of circulating endothelial progenitor cells in patients with idiopathic pulmonary arterial hypertension. *Respir Med* 2008; **102**: 1073-1079
44 **Hansmann G**, Plouffe BD, Hatch A, von Gise A, Sallmon H, Zamanian RT, Murthy SK. Design and validation of an endothelial progenitor cell capture chip and its application in patients with pulmonary arterial hypertension. *J Mol Med* (Berl) 2011; **89**: 971-983
45 **Toshner M**, Voswinckel R, Southwood M, Al-Lamki R, Howard LS, Marchesan D, Yang J, Suntharalingam J, Soon E, Exley A, Stewart S, Hecker M, Zhu Z, Gehling U, Seeger W, Pepke-Zaba J, Morrell NW. Evidence of dysfunction of endothelial progenitors in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2009; **180**: 780-787
46 **Smadja DM**, Mauge L, Sanchez O, Silvestre JS, Guerin C, Godier A, Henno P, Gaussem P, Israël-Biet D. Distinct patterns of circulating endothelial cells in pulmonary hypertension. *Eur Respir J* 2010; **36**: 1284-1293
47 **Rafat N**, Hanusch C, Brinkkoetter PT, Schulte J, Brade J, Zijlstra JG, van der Woude FJ, van Ackern K, Yard BA, Beck GCh. Increased circulating endothelial progenitor cells in septic patients: correlation with survival. *Crit Care Med* 2007; **35**: 1677-1684
48 **Burnham EL**, Taylor WR, Quyyumi AA, Rojas M, Brigham KL, Moss M. Increased circulating endothelial progenitor cells are associated with survival in acute lung injury. *Am J Respir Crit Care Med* 2005; **172**: 854-860
49 **Mutunga M**, Fulton B, Bullock R, Batchelor A, Gascoigne A, Gillespie JI, Baudouin SV. Circulating endothelial cells in patients with septic shock. *Am J Respir Crit Care Med* 2001; **163**: 195-200
50 **Tsaganos T**, Giamarellos-Bourboulis EJ, Kollias S, Zervakis D, Karagianni V, Pelekanou A, Tampaki EC, Kontogiorgi M, Koroneos A, Drakoulis N, Armaganidis A, Roussos C, Giamarellou H. Kinetics of progenitor hemopoetic stem cells in sepsis: correlation with patients survival? *BMC Infect Dis* 2006; **6**: 142
51 **Burnham EL**, Mealer M, Gaydos J, Majka S, Moss M. Acute lung injury but not sepsis is associated with increased colony formation by peripheral blood mononuclear cells. *Am J Respir Cell Mol Biol* 2010; **43**: 326-333
52 **Peinado VI**, Ramírez J, Roca J, Rodriguez-Roisin R, Barberà JA. Identification of vascular progenitor cells in pulmonary arteries of patients with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2006; **34**: 257-263
53 **Fadini GP**, Schiavon M, Cantini M, Baesso I, Facco M, Miorin M, Tassinato M, de Kreutzenberg SV, Avogaro A, Agostini C. Circulating progenitor cells are reduced in patients with severe lung disease. *Stem Cells* 2006; **24**: 1806-1813

54 **Palange P**, Testa U, Huertas A, Calabrò L, Antonucci R, Petrucci E, Pelosi E, Pasquini L, Satta A, Morici G, Vignola MA, Bonsignore MR. Circulating haemopoietic and endothelial progenitor cells are decreased in COPD. *Eur Respir J* 2006; **27**: 529-541

55 **Sala E**, Villena C, Balaguer C, Ríos A, Fernández-Palomeque C, Cosío BG, García J, Noguera A, Agustí A. Abnormal levels of circulating endothelial progenitor cells during exacerbations of COPD. *Lung* 2010; **188**: 331-338

56 **Takahashi T**, Suzuki S, Kubo H, Yamaya M, Kurosawa S, Kato M. Impaired endothelial progenitor cell mobilization and colony-forming capacity in chronic obstructive pulmonary disease. *Respirology* 2011; **16**: 680-687

57 **Martin K**, Stanchina M, Kouttab N, Harrington EO, Rounds S. Circulating endothelial cells and endothelial progenitor cells in obstructive sleep apnea. *Lung* 2008; **186**: 145-150

58 **El Solh AA**, Akinnusi ME, Berim IG, Peter AM, Paasch LL, Szarpa KR. Hemostatic implications of endothelial cell apoptosis in obstructive sleep apnea. *Sleep Breath* 2008; **12**: 331-337

59 **de la Peña M**, Barceló A, Barbe F, Piérola J, Pons J, Rimbau E, Ayllón O, Agustí AG. Endothelial function and circulating endothelial progenitor cells in patients with sleep apnea syndrome. *Respiration* 2008; **76**: 28-32

60 **El Solh AA**, Akinnusi ME, Baddoura FH, Mankowski CR. Endothelial cell apoptosis in obstructive sleep apnea: a link to endothelial dysfunction. *Am J Respir Crit Care Med* 2007; **175**: 1186-1191

61 **Loomans CJ**, De Koning EJ, Staal FJ, Rabelink TJ, Zonneveld AJ. Endothelial progenitor cell dysfunction in type 1 diabetes: another consequence of oxidative stress? *Antioxid Redox Signal* 2005; **7**: 1468-1475

62 **Sibal L**, Aldibbiat A, Agarwal SC, Mitchell G, Oates C, Razvi S, Weaver JU, Shaw JA, Home PD. Circulating endothelial progenitor cells, endothelial function, carotid intima-media thickness and circulating markers of endothelial dysfunction in people with type 1 diabetes without macrovascular disease or microalbuminuria. *Diabetologia* 2009; **52**: 1464-1473

63 **Fadini GP**, Avogaro A. It is all in the blood: the multifaceted contribution of circulating progenitor cells in diabetic complications. *Exp Diabetes Res* 2012; **2012**: 742976

64 **Tepper OM**, Galiano RD, Capla JM, Kalka C, Gagne PJ, Jacobowitz GR, Levine JP, Gurtner GC. Human endothelial progenitor cells from type II diabetics exhibit impaired proliferation, adhesion, and incorporation into vascular structures. *Circulation* 2002; **106**: 2781-2786

65 **Reinhard H**, Jacobsen PK, Lajer M, Pedersen N, Billestrup N, Mandrup-Poulsen T, Parving HH, Rossing P. Multifactorial treatment increases endothelial progenitor cells in patients with type 2 diabetes. *Diabetologia* 2010; **53**: 2129-2133

66 **Ghani U**, Shuaib A, Salam A, Nasir A, Shuaib U, Jeerakathil T, Sher F, O'Rourke F, Nasser AM, Schwindt B, Todd K. Endothelial progenitor cells during cerebrovascular disease. *Stroke* 2005; **36**: 151-153

67 **Yip HK**, Chang LT, Chang WN, Lu CH, Liou CW, Lan MY, Liu JS, Youssef AA, Chang HW. Level and value of circulating endothelial progenitor cells in patients after acute ischemic stroke. *Stroke* 2008; **39**: 69-74

68 **Taguchi A**, Matsuyama T, Moriwaki H, Hayashi T, Hayashida K, Nagatsuka K, Todo K, Mori K, Stern DM, Soma T, Naritomi H. Circulating CD34-positive cells provide an index of cerebrovascular function. *Circulation* 2004; **109**: 2972-2975

69 **Chu K**, Jung KH, Lee ST, Park HK, Sinn DI, Kim JM, Kim DH, Kim JH, Kim SJ, Song EC, Kim M, Lee SK, Roh JK. Circulating endothelial progenitor cells as a new marker of endothelial dysfunction or repair in acute stroke. *Stroke* 2008; **39**: 1441-1447

70 **Sobrino T**, Hurtado O, Moro MA, Rodríguez-Yáñez M, Castellanos M, Brea D, Moldes O, Blanco M, Arenillas JF, Leira R, Dávalos A, Lizasoain I, Castillo J. The increase of circulating endothelial progenitor cells after acute ischemic stroke is associated with good outcome. *Stroke* 2007; **38**: 2759-2764

71 **Delva P**, De Marchi S, Prior M, Degan M, Lechi A, Trettene M, Arosio E. Endothelial progenitor cells in patients with severe peripheral arterial disease. *Endothelium* 2008; **15**: 246-253

72 **Morishita T**, Uzui H, Nakano A, Mitsuke Y, Geshi T, Ueda T, Lee JD. Number of endothelial progenitor cells in peripheral artery disease as a marker of severity and association with pentraxin-3, malondialdehyde-modified low-density lipoprotein and membrane type-1 matrix metalloproteinase. *J Atheroscler Thromb* 2012; **19**: 149-158

73 **Mandraffino G**, Sardo MA, Riggio S, Loddo S, Imbalzano E, Alibrandi A, Saitta C, Cinquegrani M, Mormina EM, Saitta A. Circulating progenitor cells are increased in newly diagnosed untreated hypertensive patients with arterial stiffening but normal carotid intima-media thickness. *Hypertens Res* 2011; **34**: 876-883

74 **Giannotti G**, Doerries C, Mocharla PS, Mueller MF, Bahlmann FH, Horvàth T, Jiang H, Sorrentino SA, Steenken N, Manes C, Marzilli M, Rudolph KL, Lüscher TF, Drexler H, Landmesser U. Impaired endothelial repair capacity of early endothelial progenitor cells in prehypertension: relation to endothelial dysfunction. *Hypertension* 2010; **55**: 1389-1397

75 **Müller-Ehmsen J**, Braun D, Schneider T, Pfister R, Worm N, Wielckens K, Scheid C, Frommolt P, Flesch M. Decreased number of circulating progenitor cells in obesity: beneficial effects of weight reduction. *Eur Heart J* 2008; **29**: 1560-1568

76 **MacEneaney OJ**, Kushner EJ, Van Guilder GP, Greiner JJ, Stauffer BL, DeSouza CA. Endothelial progenitor cell number and colony-forming capacity in overweight and obese adults. *Int J Obes* (Lond) 2009; **33**: 219-225

77 **Tobler K**, Freudenthaler A, Baumgartner-Parzer SM, Wolzt M, Ludvik B, Nansalmaa E, Nowotny PJ, Seidinger D, Steiner S, Luger A, Artwohl M. Reduction of both number and proliferative activity of human endothelial progenitor cells in obesity. *Int J Obes* (Lond) 2010; **34**: 687-700

78 **MacEneaney OJ**, Kushner EJ, Westby CM, Cech JN, Greiner JJ, Stauffer BL, DeSouza CA. Endothelial progenitor cell function, apoptosis, and telomere length in overweight/obese humans. *Obesity* (Silver Spring) 2010; **18**: 1677-1682

79 **Heida NM**, Müller JP, Cheng IF, Leifheit-Nestler M, Faustin V, Riggert J, Hasenfuss G, Konstantinides S, Schäfer K. Effects of obesity and weight loss on the functional properties of early outgrowth endothelial progenitor cells. *J Am Coll Cardiol* 2010; **55**: 357-367

80 **Hambrecht R**, Niebauer J, Marburger C, Grunze M, Kälberer B, Hauer K, Schlierf G, Kübler W, Schuler G. Various intensities of leisure time physical activity in patients with coronary artery disease: effects on cardiorespiratory fitness and progression of coronary atherosclerotic lesions. *J Am Coll Cardiol* 1993; **22**: 468-477

81 **Tanaka H**, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. *Circulation* 2000; **102**: 1270-1275

82 **Kozakova M**, Palombo C, Mhamdi L, Konrad T, Nilsson P, Staehr PB, Paterni M, Balkau B. Habitual physical activity and vascular aging in a young to middle-age population at low cardiovascular risk. *Stroke* 2007; **38**: 2549-2555

83 **Seals DR**, Desouza CA, Donato AJ, Tanaka H. Habitual exercise and arterial aging. *J Appl Physiol* 2008; **105**: 1323-1332

84 **Kojda G**, Cheng YC, Burchfield J, Harrison DG. Dysfunctional regulation of endothelial nitric oxide synthase (eNOS) expression in response to exercise in mice lacking one eNOS gene. *Circulation* 2001; **103**: 2839-2844

85 **Jasperse JL**, Laughlin MH. Endothelial function and exercise training: evidence from studies using animal models. *Med Sci Sports Exerc* 2006; **38**: 445-454

86 **Laughlin MH**. Joseph B. Wolfe Memorial lecture. Physical

activity in prevention and treatment of coronary disease: the battle line is in exercise vascular cell biology. *Med Sci Sports Exerc* 2004; **36**: 352-362

87 **Hambrecht R**, Walther C, Möbius-Winkler S, Gielen S, Linke A, Conradi K, Erbs S, Kluge R, Kendziorra K, Sabri O, Sick P, Schuler G. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation* 2004; **109**: 1371-1378

88 **Belardinelli R**, Paolini I, Cianci G, Piva R, Georgiou D, Purcaro A. Exercise training intervention after coronary angioplasty: the ETICA trial. *J Am Coll Cardiol* 2001; **37**: 1891-1900

89 **Hornig B**, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. *Circulation* 1996; **93**: 210-214

90 **Stewart KJ**, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med* 2002; **347**: 1941-1951

91 **Stewart KJ**. Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension: plausible mechanisms for improving cardiovascular health. *JAMA* 2002; **288**: 1622-1631

92 **Wannamethee SG**, Lowe GD, Whincup PH, Rumley A, Walker M, Lennon L. Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation* 2002; **105**: 1785-1790

93 **Tjønna AE**, Lee SJ, Rognmo Ø, Stølen TO, Bye A, Haram PM, Loennechen JP, Al-Share QY, Skogvoll E, Slørdahl SA, Kemi OJ, Najjar SM, Wisløff U. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation* 2008; **118**: 346-354

94 **Moholdt T**, Wisløff U, Nilsen TI, Slørdahl SA. Physical activity and mortality in men and women with coronary heart disease: a prospective population-based cohort study in Norway (the HUNT study). *Eur J Cardiovasc Prev Rehabil* 2008; **15**: 639-645

95 **Wisløff U**, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, Tjønna AE, Helgerud J, Slørdahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen Ø, Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation* 2007; **115**: 3086-3094

96 **Dimopoulos S**, Anastasiou-Nana M, Sakellariou D, Drakos S, Kapsimalakou S, Maroulidis G, Roditis P, Papazachou O, Vogiatzis I, Roussos C, Nanas S. Effects of exercise rehabilitation program on heart rate recovery in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006; **13**: 67-73

97 **Meyer K**, Foster C, Georgakopoulos N, Hajric R, Westbrook S, Ellestad A, Tilman K, Fitzgerald D, Young H, Weinstein H, Roskamm H. Comparison of left ventricular function during interval versus steady-state exercise training in patients with chronic congestive heart failure. *Am J Cardiol* 1998; **82**: 1382-1387

98 **Beckers PJ**, Denollet J, Possemiers NM, Wuyts FL, Vrints CJ, Conraads VM. Combined endurance-resistance training vs. endurance training in patients with chronic heart failure: a prospective randomized study. *Eur Heart J* 2008; **29**: 1858-1866

99 **Anagnostakou V**, Chatzimichail K, Dimopoulos S, Karatzanos E, Papazachou O, Tasoulis A, Anastasiou-Nana M, Roussos C, Nanas S. Effects of interval cycle training with or without strength training on vascular reactivity in heart failure patients. *J Card Fail* 2011; **17**: 585-591

100 **Gerovasili V**, Drakos S, Kravari M, Malliaras K, Karatzanos E, Dimopoulos S, Tasoulis A, Anastasiou-Nana M, Roussos C, Nanas S. Physical exercise improves the peripheral microcirculation of patients with chronic heart failure. *J Cardiopulm Rehabil Prev* 2009; **29**: 385-391

101 **Laufs U**, Werner N, Link A, Endres M, Wassmann S, Jürgens K, Miche E, Böhm M, Nickenig G. Physical training increases endothelial progenitor cells, inhibits neointima formation, and enhances angiogenesis. *Circulation* 2004; **109**: 220-226

102 **Yang Z**, Xia WH, Su C, Wu F, Zhang YY, Xu SY, Liu X, Zhang XY, Ou ZJ, Lai GH, Liao XX, Jin YF, Tao J. Regular exercise-induced increased number and activity of circulating endothelial progenitor cells attenuates age-related decline in arterial elasticity in healthy men. *Int J Cardiol* 2011 Sep 26; Epub ahead of print

103 **Rakobowchuk M**, Harris E, Taylor A, Baliga V, Cubbon RM, Rossiter HB, Birch KM. Heavy and moderate interval exercise training alters low-flow-mediated constriction but does not increase circulating progenitor cells in healthy humans. *Exp Physiol* 2012; **97**: 375-385

104 **Walther C**, Gaede L, Adams V, Gelbrich G, Leichtle A, Erbs S, Sonnabend M, Fikenzer K, Körner A, Kiess W, Bruegel M, Thiery J, Schuler G. Effect of increased exercise in school children on physical fitness and endothelial progenitor cells: a prospective randomized trial. *Circulation* 2009; **120**: 2251-2259

105 **Witkowski S**, Lockard MM, Jenkins NT, Obisesan TO, Spangenburg EE, Hagberg JM. Relationship between circulating progenitor cells, vascular function and oxidative stress with long-term training and short-term detraining in older men. *Clin Sci* (Lond) 2010; **118**: 303-311

106 **Haram PM**, Kemi OJ, Wisloff U. Adaptation of endothelium to exercise training: insights from experimental studies. *Front Biosci* 2008; **13**: 336-346

107 **Ajijola OA**, Dong C, Herderick EE, Ma Q, Goldschmidt-Clermont PJ, Yan Z. Voluntary running suppresses proinflammatory cytokines and bone marrow endothelial progenitor cell levels in apolipoprotein-E-deficient mice. *Antioxid Redox Signal* 2009; **11**: 15-23

108 **Itoh T**, Imano M, Nishida S, Tsubaki M, Hashimoto S, Ito A, Satou T. Exercise increases neural stem cell proliferation surrounding the area of damage following rat traumatic brain injury. *J Neural Transm* 2011; **118**: 193-202

109 **Luk TH**, Dai YL, Siu CW, Yiu KH, Chan HT, Lee SW, Li SW, Fong B, Wong WK, Tam S, Lau CP, Tse HF. Effect of exercise training on vascular endothelial function in patients with stable coronary artery disease: a randomized controlled trial. *Eur J Prev Cardiol* 2012; **19**: 830-839

110 **Cesari F**, Marcucci R, Gori AM, Burgisser C, Francini S, Sofi F, Gensini GF, Abbate R, Fattirolli F. Impact of a cardiac rehabilitation program and inflammatory state on endothelial progenitor cells in acute coronary syndrome patients. *Int J Cardiol* 2012 May 22; Epub ahead of print

111 **Manfredini F**, Rigolin GM, Malagoni AM, Catizone L, Mandini S, Sofritti O, Mauro E, Soffritti S, Boari B, Cuneo A, Zamboni P, Manfredini R. Exercise training and endothelial progenitor cells in haemodialysis patients. *J Int Med Res* 2009; **37**: 534-540

112 **Sarto P**, Balducci E, Balconi G, Fiordaliso F, Merlo L, Tuzzato G, Pappagallo GL, Frigato N, Zanocco A, Forestieri C, Azzarello G, Mazzucco A, Valenti MT, Alborino F, Noventa D, Vinante O, Pascotto P, Sartore S, Dejana E, Latini R. Effects of exercise training on endothelial progenitor cells in patients with chronic heart failure. *J Card Fail* 2007; **13**: 701-708

113 **Van Craenenbroeck EM**, Hoymans VY, Beckers PJ, Possemiers NM, Wuyts K, Paelinck BP, Vrints CJ, Conraads VM. Exercise training improves function of circulating angiogenic cells in patients with chronic heart failure. *Basic Res Cardiol* 2010; **105**: 665-676

114 **Gatta L**, Armani A, Iellamo F, Consoli C, Molinari F, Caminiti G, Volterrani M, Rosano GM. Effects of a short-term exercise training on serum factors involved in ventricular remodelling in chronic heart failure patients. *Int J Cardiol* 2012; **155**: 409-413

115 **Erbs S**, Höllriegel R, Linke A, Beck EB, Adams V, Gielen

S, Möbius-Winkler S, Sandri M, Kränkel N, Hambrecht R, Schuler G. Exercise training in patients with advanced chronic heart failure (NYHA IIIb) promotes restoration of peripheral vasomotor function, induction of endogenous regeneration, and improvement of left ventricular function. *Circ Heart Fail* 2010; **3**: 486-494

116 **Mezzani A**, Grassi B, Jones AM, Giordano A, Corrà U, Porcelli S, Della Bella S, Taddeo A, Giannuzzi P. Speeding of pulmonary VO(2) on-kinetics by light-to-moderate-intensity aerobic exercise training in chronic heart failure: Clinical and pathophysiological correlates. *Int J Cardiol* 2012 Jun 15; Epub ahead of print

117 **Schlager O**, Giurgea A, Schuhfried O, Seidinger D, Hammer A, Gröger M, Fialka-Moser V, Gschwandtner M, Koppensteiner R, Steiner S. Exercise training increases endothelial progenitor cells and decreases asymmetric dimethylarginine in peripheral arterial disease: a randomized controlled trial. *Atherosclerosis* 2011; **217**: 240-248

118 **Cesari F**, Sofi F, Gori AM, Corsani I, Capalbo A, Caporale R, Abbate R, Gensini GF, Casini A. Physical activity and circulating endothelial progenitor cells: an intervention study. *Eur J Clin Invest* 2012; **42**: 927-932

119 **Fukai T**, Siegfried MR, Ushio-Fukai M, Cheng Y, Kojda G, Harrison DG. Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. *J Clin Invest* 2000; **105**: 1631-1639

120 **Rehman J**, Li J, Parvathaneni L, Karlsson G, Panchal VR, Temm CJ, Mahenthiran J, March KL. Exercise acutely increases circulating endothelial progenitor cells and monocyte-/macrophage-derived angiogenic cells. *J Am Coll Cardiol* 2004; **43**: 2314-2318

121 **Yang Z**, Wang JM, Chen L, Luo CF, Tang AL, Tao J. Acute exercise-induced nitric oxide production contributes to upregulation of circulating endothelial progenitor cells in healthy subjects. *J Hum Hypertens* 2007; **21**: 452-460

122 **Thorell D**, Borjesson M, Larsson P, Ulfhammer E, Karlsson L, DuttaRoy S. Strenuous exercise increases late outgrowth endothelial cells in healthy subjects. *Eur J Appl Physiol* 2009; **107**: 481-488

123 **Möbius-Winkler S**, Hilberg T, Menzel K, Golla E, Burman A, Schuler G, Adams V. Time-dependent mobilization of circulating progenitor cells during strenuous exercise in healthy individuals. *J Appl Physiol* 2009; **107**: 1943-1950

124 **Lockard MM**, Witkowski S, Jenkins NT, Spangenburg EE, Obisesan TO, Hagberg JM. Thrombin and exercise similarly influence expression of cell cycle genes in cultured putative endothelial progenitor cells. *J Appl Physiol* 2010; **108**: 1682-1690

125 **Van Craenenbroeck EM**, Vrints CJ, Haine SE, Vermeulen K, Goovaerts I, Van Tendeloo VF, Hoymans VY, Conraads VM. A maximal exercise bout increases the number of circulating CD34+/KDR+ endothelial progenitor cells in healthy subjects. Relation with lipid profile. *J Appl Physiol* 2008; **104**: 1006-1013

126 **Laufs U**, Urhausen A, Werner N, Scharhag J, Heitz A, Kissner G, Böhm M, Kindermann W, Nickenig G. Running exercise of different duration and intensity: effect on endothelial progenitor cells in healthy subjects. *Eur J Cardiovasc Prev Rehabil* 2005; **12**: 407-414

127 **Adams V**, Linke A, Breuckmann F, Leineweber K, Erbs S, Kränkel N, Bröcker-Preuss M, Woitek F, Erbel R, Heusch G, Hambrecht R, Schuler G, Möhlenkamp S. Circulating progenitor cells decrease immediately after marathon race in advanced-age marathon runners. *Eur J Cardiovasc Prev Rehabil* 2008; **15**: 602-607

128 **Bonsignore MR**, Morici G, Riccioni R, Huertas A, Petrucci E, Veca M, Mariani G, Bonanno A, Chimenti L, Gioia M, Palange P, Testa U. Hemopoietic and angiogenetic progenitors in healthy athletes: different responses to endurance and maximal exercise. *J Appl Physiol* 2010; **109**: 60-67

129 **Goussetis E**, Spiropoulos A, Tsironi M, Skenderi K, Margeli A, Graphakos S, Baltopoulos P, Papassotiriou I. Spartathlon, a 246 kilometer foot race: effects of acute inflammation induced by prolonged exercise on circulating progenitor reparative cells. *Blood Cells Mol Dis* 2009; **42**: 294-299

130 **Shaffer RG**, Greene S, Arshi A, Supple G, Bantly A, Moore JS, Parmacek MS, Mohler ER. Effect of acute exercise on endothelial progenitor cells in patients with peripheral arterial disease. *Vasc Med* 2006; **11**: 219-226

131 **Van Craenenbroeck EM**, Beckers PJ, Possemiers NM, Wuyts K, Frederix G, Hoymans VY, Wuyts F, Paelinck BP, Vrints CJ, Conraads VM. Exercise acutely reverses dysfunction of circulating angiogenic cells in chronic heart failure. *Eur Heart J* 2010; **31**: 1924-1934

132 **Van Craenenbroeck EM**, Bruyndonckx L, Van Berckelaer C, Hoymans VY, Vrints CJ, Conraads VM. The effect of acute exercise on endothelial progenitor cells is attenuated in chronic heart failure. *Eur J Appl Physiol* 2011; **111**: 2375-2379

133 **Sandri M**, Adams V, Gielen S, Linke A, Lenk K, Kränkel N, Lenz D, Erbs S, Scheinert D, Mohr FW, Schuler G, Hambrecht R. Effects of exercise and ischemia on mobilization and functional activation of blood-derived progenitor cells in patients with ischemic syndromes: results of 3 randomized studies. *Circulation* 2005; **111**: 3391-3399

S- Editor Cheng JX **L- Editor** Kerr C **E- Editor** Li JY