RESEARCH LETTER

Is there a relationship between exercise--induced endothelial progenitor cell mobilization and cytokine concentrations in patients with premature coronary heart disease?

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Introduction Coronary artery disease (CAD) is currently one of the most important causes of morbidity and mortality. Research on the development and course of CAD underlines the important role of biochemical markers and prothrombotic factors, such as high-sensitive C-reactive protein and cytokines.[1] Cytokines affect the growth, proliferation, and activation of hematopoietic cells and cells involved in cellular and humoral response. Interleukin 18 (IL-18) belongs to a group of cytokines with proinflammatory properties. It stimulates lymphocytes T and natural killer cells and modulates the action of other factors involved in atherogenesis. It is also an independent index for the risk of coronary events and cardiovascular death.[2] Hepatocyte growth factor (HGF) is a cytokine that stimulates c-met tyrosine kinase, thus inducing angiogenesis and tissue regeneration. An increase in blood HGF levels has been confirmed in hypertension, obesity, and CAD.[3]

Stem cell factor (SCF) stimulates the differentiation of $CD34^+$ cells. Kuang et al.[4] proved that myocardial infarction induces SCF expression in the injured area of the myocardial muscle, inducing migration of myocardial stem cells to the infarction area. Stromal-derived factor 1 (SDF-1) activates and directly affects leukocyte migration and induces platelet aggregation. A number of authors reported increased SDF-1 concentrations in patients with acute coronary syndrome and a positive correlation with a number of circulating endothelial progenitor cells (EPCs); others observed lower SDF-1 concentrations both in patients with non-ST-elevation myocardial infarction and in the control group of healthy subjects.[5] The characteristic features of EPCs are vitality as well as the ability to form colonies in vitro and differentiate into mature endothelial cells. The beneficial effects of EPCs might be explained by the paracrine effects of growth factors, chemokines, and cytokines, which are released from the cells.[6] It seems that the paracrine effects of EPCs could be used to optimize cell-based therapies, which could be achieved by an ex-vivo manipulation of the cells to improve the secretion of proregenerative factors. Cytokines and chemokines have angiopoietic, trophic, and antiapoptotic effects.[6]

Hill et al.[7] reported an association between the number of circulating EPCs and endothelial function. They showed that a decrease in EPCs circulating in peripheral blood was correlated with the progression of cardiovascular diseases.

Kazmierski et al.[8] found that the number of circulating EPCs in peripheral blood at rest does not differ between individuals with premature atherosclerosis and healthy controls. Physical exercise in both groups was linked to increased concentrations of EPCs. In patients with premature CAD, EPC mobilization after exercise was delayed.

The present study is a continuation of the above research. We aimed to evaluate potential correlations between IL-18, SDF-1, HGF, and SCF levels in patients with premature CAD and exercise-induced EPC mobilization. We selected those chemotactic substances because each of them has a different effect on the process of atherogenesis.

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TABLE Number and exercise-induced mobilization of endothelial progenitor cells

	Study group n = 60	Control group n = 33	*P* value
exercise, METs	9.9 (2.7–12)	10.1 (5.2–10.2)	0.07
EPC 0[a]	2.1 (0–6.3)	2.0 (0–5.1)	0.96
EPC 15[a]	2.1 (0.5–4.9)	3.5 (1.3–5.6)	<0.00001
EPC 60[a]	3.2 (0.6–7.4)	2.7 (1–4.8)	0.1
EPC 15 – EPC 0[b]	0.2 (–1.6 to 2)	1.5 (–1.1 to 4.1)	<0.00001
EPC 60 – EPC 0[c]	1.1 (–1.4 to 4.3)	0.8 (–3.4 to 3.1)	0.17

Data are presented as median and interquartile range.

a number of EPC/μl
b mobilization 15, difference between EPC number at rest and 15 minutes after exercise
c mobilization 60, difference between EPC number at rest and 60 minutes after exercise

Abbreviations: EPC, endothelial progenitor cells; MET, metabolic equivalents

Patients and methods The study included 60 consecutive subjects (49 men and 11 women; mean age, 43 years) with stable CAD (Canadian Cardiovascular Society [CCS] ≤II). The inclusion criteria were as follows: age, 18–50 years; the presence of CAD diagnosed before the age of 45 years and the presence of at least 1 shift that tapered >70% in at least 1 of the 3 major epicardial arteries; New York Heart Association class I; stable CAD (CCS ≤II); and written consent to participate in the study. All patients underwent coronary angioplasty at least 1 year earlier. None of the patients received clopidogrel or antiplatelet drugs other than acetylsalicylic acid. The control group consisted of 33 healthy volunteers matched for age and sex.

The study protocol included a medical history and physical examination, echocardiography, cardiac stress test, and, additionally, coronary angiography in the study group. The number of EPCs was determined according to the recommendations of the International Society for Hematotherapy and Graft Engineering using flow cytometry (FACS Calibur, Beckton Dickinson, New Jersey, United States), and the results were expressed in 1 microliter (com/μl).[9] Moreover, plasma IL-18, SDF-1, HGF, and SCF levels were assessed using venous blood. Blood samples were taken in the morning, in the fasting state, from the peripheral vein using the vacuum system for test-tubes with EDTA.

Results In the study group, the number of circulating EPCs at rest did not differ from that observed 15 minutes after exercise; however, it increased significantly 60 minutes after exercise (TABLE). In the control group, the number of EPCs increased significantly 15 minutes after exercise, but the number of circulating EPCs 60 minutes after exercise was smaller than that recorded 15 minutes after exercise, although it was still greater from that at rest (TABLE). The number of EPCs at rest and 60 minutes after exercise did not differ significantly between the study and control groups; on the contrary, the number of EPCs 15 minutes after exercise was significantly smaller in the study group compared with the control group (TABLE).

During the exercise stress test, none of the groups showed any electrocardiographic features of myocardial ischemia. In the study group, significantly higher IL-18 concentrations in peripheral blood were observed compared with the control group (P = 0.00 003); however, no correlation was found between IL-18 levels and the number of EPCs at rest or its mobilization 15 and 60 minutes after exercise either in the study group or in the control group. HGF concentrations in the study group were significantly higher (P = 0.0002) and SCF concentrations were significantly lower (P = 0.02) compared with the control group. Plasma SDF-1 concentrations were comparable in both groups (P = 0.07). Moreover, no correlation was found between HGF, SDF-1, and SCF concentrations and the number of EPCs at rest and the number and mobilization of EPCs 15 and 60 minutes after exercise either in the study group or in the control group. In the control group, the number of EPCs was positively correlated with SCF concentrations. A significant increase in circulating EPCs and an increase in the SCF concentration 15 minutes after exercise were observed (r = 0.36; P = 0.04).

We also studied the concentrations of IL-18, SDF-1, HGF, and SCF and their potential associations with exercise-induced mobilization of EPCs. Blood IL-18 and HGF concentrations were significantly higher in the study group compared with the control group. Blood SCF concentrations were lower in the study group compared with the control group, and plasma SDF-1 concentrations were comparable in both groups. However, no statistically significant relationship between the number and exercise-induced mobilization of EPCs and IL-18, HGF, or SDF-1 was shown. In the control group, a positive correlation between SCF levels and the number of EPCs 15 minutes after exercise was observed. Moreover, there was no difference in the number of circulating EPCs at rest between patients with stable CAD and the control group. However, the control group was characterized by a significant increase in the number of EPCs

15 minutes after exercise and its quick decrease after another 45 minutes. The changes in the number of circulating EPCs in patients with premature CAD were completely different. The number of circulating EPCs 15 minutes after exercise remained unchanged, although 60 minutes after exercise, a significant increase in the number of EPCs was observed in comparison with the number at rest.

Numerous studies have shown exercise-induced mobilization of EPCs in peripheral blood after a single intense exercise protocol. Adams et al.[10] studied the mobilization of EPCs in a larger group of patients with CAD and positive exercise stress test results, who had undergone coronary angioplasty in the past. They showed a significant increase in the number of EPCs only in the group of patients with confirmed CAD, in which the exercise was the reason for ischemic changes on an electrocardiogram. Adams et al.[10] did not report a significant difference in the number of EPCs between the group of patients after coronary revascularization and the control group either at rest or after exercise mobilization. Other studies also confirmed exercise-induced EPC mobilization.[11,12]

In conclusion, physical exercise causes a significant increase in the number of circulating EPCs; however, in patients with CAD, exercise-induced EPC mobilization is delayed.

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