Time-dependent mobilization of circulating progenitor cells during strenuous exercise in healthy individuals

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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 107: 1943–1950, 2009. First published October 1, 2009; doi:10.1152/japplphysiol.00532.2009.—Exercise stimulates the release of hematopoietic and endothelial progenitor cells (EPC) from the bone marrow. However, no data are available concerning the time frame of EPC release during strenuous exercise. The aim of the present study was to investigate the time-dependent release of progenitor cells during strenuous exercise. Eighteen healthy young men cycled for 4 h continuously at 70% of their individual anaerobic threshold. Peripheral blood was drawn at 16 predefined time points during and after finishing cycling. A significant rise in heart rate and leukocytes was obvious, whereas lactate levels and hematocrit did not change. The amount of circulating progenitor cells, EPCs, mature endothelial cells (mECs), and microparticles, quantified by flow cytometry, showed a significant time-dependent increase at 210/240 min. In addition a very early rise in VEGF and later increase in IL-6, both measured by ELISA, were evident. All observed changes were normalized 24 h after finishing the test. In conclusion, strenuous activity in healthy individuals leads to a time-dependent increase in mECs, PCs, and EPCs that may be related to VEGF and IL-6.

endothelial progenitor cells; vascular endothelial growth factor

THE CRUCIAL ROLE played by the endothelium in cardiovascular biology is becoming increasingly appreciated (17). Endothelial dysfunction appears to have detrimental functional consequences as well as adverse long-term effects. Indeed, endothelial injury has been implicated in atherosclerosis, thrombosis, and hypertension. Even in obese otherwise healthy children endothelial dysfunction is detectable (40), and the balance between endothelial injury and endothelial recovery is of paramount importance for reducing cardiovascular events (18). However, mature endothelial cells possess limited regenerative capacity (16). During the last 10 years, it became evident that endothelial progenitor cells (EPCs), liberated from the bone marrow, play an important role in maintaining an intact endothelial cell layer either by secretion of mediators of proliferation and migration, or survival factors (36).

Besides humoral factors such as cytokines (4, 43), hormones (10), chemokines (49) and drugs (15, 47), exercise has been shown to increase the number of circulating EPCs (1, 30, 31, 37, 46). It is hypothesized in the current literature that exercise-induced mobilization of EPCs from the bone marrow may be due to shear activated endothelial nitric oxide synthase (eNOS) activity in the endothelium followed by an increase in nitric oxide (3) or to an elevated level of VEGF (4, 28). In most of the studies analyzing the impact of exercise on the amount of circulating progenitor cells, the study population performed a single symptom-limited cardiopulmonary maximal exercise test, and the concentration of EPCs was determined before and directly after the test (39, 46, 48) or for up to 144 h past the maximal stress test (1). At least in two studies analyzing the concentration of EPCs before and directly after a maximal cardiopulmonary exercise test a significant increase of ~50% was documented (39, 46). Analyzing the influence of a longer strenuous exercise, like running a marathon or a longer race, on the concentration of circulating progenitor cells, only three studies are available (2, 7, 22). In one study the concentration of CD34pos hematopoietic stem cells was not influenced when measured before and directly after finishing a marathon (7), whereas the other study in advanced-age marathon runners demonstrated a significant downregulation of CD34pos cells and no change in the concentration of EPCs (2). In a recently published study by Gousseitis and coworkers (22), a 10-fold increase in EPCs measured by colony-forming units after a 246-km foot race has been documented. A factor mediating the mobilization of EPCs from the bone marrow is vascular endothelial growth factor (VEGF). Gene transfer of VEGF enhances the population of circulating EPCs by a factor of 2 to 4 over baseline, and exercise has been documented to increase VEGF (1, 4). IL-6, another factor possibly influencing EPC content, stimulates EPC proliferation, migration, and tube formation on matrigel (20). No data are available demonstrating a direct effect of IL-6 on the mobilization of EPCs from the bone marrow.

Based on the available studies, no conclusive picture on the mobilization of progenitor cells after strenuous activity can be drawn. Absolutely no data are available in the current literature looking at the concentration of progenitor cells during strenuous exercise. Therefore, the aim of the present study was to answer the following questions: 1) What is the response of hematopoietic and endothelial progenitor cells after a stan-
dardized prolonged endurance exercise? and 2) What is the kinetic of cell mobilization during this standardized exercise?

METHODS

Participants and Study Design

The study population consisted of 18 healthy sportive men, all nonsmokers, performing exercise (especially bicycling) on a regular basis. A basic physical examination of the subjects, ECG, blood pressure, and routine laboratory status did not reveal any pathological findings. Subjects did not use any medication 8 wk before the study until the end. The study was approved by the local Ethics Committee, and all participants gave their written informed consent.

Exercise Test and Exercise Program

Maximal exercise test. One to two weeks before the main test, all subjects performed an incremental graded exercise on a cycle ergometer, starting with 50 W and an increase of 50 W every 3 min until volitional exhaustion. This test was initiated for the measurement of peak oxygen uptake (\(\dot{V}O_2\max\)) and the individual anaerobic threshold, determined according to Stegmann et al. (41). The \(\dot{V}O_2\) was measured at 0.5-min intervals using an open spirometric system. Capillary blood samples were obtained from the previously hyperemized ear lobe at rest, at the end, at each level of exercise, and at fixed time points after exercise to determine lactate concentration.

Exercise program. Two days before the main test until after the last blood sample, a diet poor of nitrate/nitrite and antioxidants was carried out by the participants to avoid nutrition effects on endothelial function and cell mobilization. The main test program included one cycle ergometer test with an individualized power of 70% of the individual anaerobic threshold (IAT), for 240 min. IAT was measured by the maximal exercise test before, as described above. During the cycle exercise, all participants got 750 ml fluid (1 liter of fluid is equal to 0.5 min) per hour, and additionally one banana per hour for standardization.

Analytical Procedures

All samples were analyzed by using clinical automatic sample analyzers. The concentration of C-reactive protein (CRP) in the serum was measured using a turbidity assay (Roche Diagnostics, Mannheim, Germany). Low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and cholesterol concentrations were measured by enzymatic in situ assays with photometric final quantification (HDL), triglycerides, and cholesterol concentrations were measured by enzymatic in situ assays with photometric final quantification (Roche Diagnostics). Size calibration was performed with nonfluorescent poly(styrene) microspheres (Invitrogen Molecular Probes, Eugene, OR).

Detection of circulating microparticles (defined as CD42b\(^{pos}\) and a size <1.5 \(\mu\)m) and endothelial microparticles [defined as CD62E\(^{pos}\) (marker of endothelial cells), CD42b\(^{pos}\) (marker for platelets), and a size <1.5 \(\mu\)m], which are considered as a vascular disease marker (27), was determined as recently described (14). Briefly, venous blood was collected into citrate-containing tubes, and platelet-poor plasma (PPP) was prepared (centrifugation for 2 min at 11,000 g). An aliquot of 100 \(\mu\)l PPP was incubated in the dark for 30 min with the following antibodies: FITC-conjugated mouse anti-human CD42b (Becton-Dickinson) and Pe-Cy5-conjugated mouse anti-human CD62E (Becton Dickinson). After incubation, sterile filtered PBS was added, and the mix was analyzed immediately by flow cytometry (LSRII, Becton-Dickinson). Size calibration was performed with nonfluorescent poly(styrene) microspheres (Invitrogen Molecular Probes, Eugene, OR).

Statistics

Data are expressed as means ± SE. Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test and compared among groups by one-way ANOVA and Tukey-Kramer multiple comparisons test. A \(P\) value ≤ 0.05 was considered statistically significant.

RESULTS

Characteristics of Study Cohort

The main characteristics and anthropometric and performance data are shown in Table 1. Table 1 demonstrates the normal blood pressure, normal blood lipids, CRP, and the good fitness level with a maximal \(\dot{V}O_2\) (\(\dot{V}O_2\max\)) of nearly 60 ml\(\cdot\)min\(^{-1}\)\(\cdot\)kg\(^{-1}\) of the subjects. All the participants were able to perform and complete a maximal graded exercise test according to the standard protocol. Most of the participants were able to complete the submaximal exercise test according to the standard protocol, and all the participants were able to complete the exercise test without any medication or dietary restrictions. The blood pressure and heart rate were measured immediately before and after the exercise test.
to complete 240 min of this individually standardized exercise with only one exception, a subject who stopped after 235 min of exercise.

Performing the 4 h of cycling at ~70% of IAT, the heart rate increased significantly over time with a maximum at 240 min (Fig. 1). At that time point the study participants reached ~81.8 ± 1.6% of the maximal heart rate achieved at the maximal cardiopulmonary exercise. Already 1 h after stopping the exercise, the heart rate values returned to baseline values (Fig. 1). During the whole cycling period, no excessive increase in serum lactate concentration was noted (data not shown), which confirms the clear aerobic character of the exercise.

Analysis of Circulating Blood Cells

Cycling for 4 h at 70% of IAT resulted in a significant time-dependent increase in leukocytes (2.5 ± 0.1-fold maximal increase vs. baseline) and thrombocytes (1.3 ± 0.03-fold maximal increase vs. baseline) beginning at 90 min or 120 min, respectively, with a maximum at 240 min (Fig. 2 and Table 2). No change in hematocrit was observed over time (Table 2). Besides a change in leukocytes and thrombocytes, a significant change was also seen in neutrophils, monocytes, and lymphocytes after 4 h cycling compared with baseline (Table 2). No change was seen in the hemoglobin concentration and in erythrocyte content (Table 2). All the observed changes were back to baseline within 24 h after the exercise stress (Table 2).

Quantification of Circulating Progenitor and Endothelial Progenitor Cells

Analyzing circulating CD34pos (Fig. 3A) and CD133pos cells (Fig. 4A), a significant time-dependent rise could be observed. For CD34pos cells a 3.1-fold increase was seen, whereas CD133pos exhibited a 2.5-fold increase.

With respect to endothelial progenitor cells, defined as CD34/KDR or CD133/KDR double positive cells, a time-dependent rise was also noted. CD34/KDR double positive cells exhibited a significant 5.5-fold increase at 240 min (Fig. 3B), whereas the maximum rise for CD133/KDR double positive cells was seen at 210 min (3.5-fold increase) (Fig. 4). After finishing the cycling stress, the increase in cell number of CD34pos, CD133pos, CD34/KDR, or CD133/KDR returned to baseline values within 24 h (Figs. 3 and 4).

Number of Circulating Mature Endothelial Cells and Microparticles

To assess if strenuous exercise excites a damage of the endothelial layer, the concentration of circulating mature CD146pos endothelial cells as well as microparticles was measured by flow cytometry. A time-dependent significant rise was observed for CD146pos cells between 120 min and 24 h postexercise, with a maximum 5.4-fold increase at 210 min compared with baseline (Fig. 5). In addition a significant positive linear correlation was evident between the maximal change in CD146pos cells and the maximal change in CD133pos (r = 0.77; P = 0.0007), or the maximal change in CD34pos (r = 0.52; P = 0.046). A trend was obvious for the maximal change in CD146pos cells and the maximal change in CD133pos/KDRpos cells (r = 0.5; P = 0.06).

With respect to the analysis of microparticles, defined as <1.5 μm in size and CD42bneg, and endothelial micropar-

Table 2. Maximal changes in blood constituents

<table>
<thead>
<tr>
<th>Blood Constituent</th>
<th>Baseline</th>
<th>At 240 min</th>
<th>24 h Postexercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>0.43</td>
<td>0.43</td>
<td>0.42</td>
</tr>
<tr>
<td>Hemoglobin, mmol/l</td>
<td>9.46±0.17</td>
<td>9.5±0.12</td>
<td>9.18±0.15</td>
</tr>
<tr>
<td>Erythrocytes, Tpt/l</td>
<td>5.00±0.08</td>
<td>5.06±0.07</td>
<td>4.83±0.07</td>
</tr>
<tr>
<td>Leukocytes, Gpt/l</td>
<td>5.14±0.23</td>
<td>12.46±0.76*</td>
<td>5.75±0.22</td>
</tr>
<tr>
<td>Thrombocytes, Gpt/l</td>
<td>216±9</td>
<td>291±12*</td>
<td>217±8</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>0.53±0.01</td>
<td>0.72±0.21</td>
<td>0.55±0.02</td>
</tr>
<tr>
<td>Monocytes, %</td>
<td>0.076±0.003</td>
<td>0.062±0.003*</td>
<td>0.080±0.005</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>0.35±0.01</td>
<td>0.20±0.01*</td>
<td>0.34±0.02</td>
</tr>
</tbody>
</table>

Values are means ± SE. Gpt, gigaparticles; Tpt, teraparticles. *P < 0.001 vs. baseline and 24 h postexercise.
Serum Levels of VEGF and IL-6

A significant 1.9-fold increase of VEGF was observed after 10 min compared with baseline (baseline: 79.8 ± 15.4 pg/ml; vs. 10 min: 132.6 ± 32.1 pg/ml; P < 0.05). This VEGF increase was no longer detectable after 15 min (Fig. 6A).

Measuring plasma IL-6 concentration, a time-dependent rise was evident over time, with a maximum at 30 min postexercise (16.5 ± 3.5-fold increase vs. baseline) (Fig. 6B). Twenty-four hours after finishing the cycling the IL-6 concentration was back to baseline values (24 h postexercise: 0.85 ± 0.18 pg/ml).

A significant positive correlation could be detected between the maximal change in VEGF and EPCs defined as CD133pos/KDRpos (r = 0.67, P = 0.0045). Analyzing the correlation between maximal change (Δ) in VEGF or IL-6 and EPCs, this time defined as CD34pos/KDRpos, no significant correlation was evident (ΔVEGF and ΔCD34pos/KDRpos; r = 0.045, P = 0.86; ΔIL-6 and ΔCD34pos/KDRpos; r = 0.28, P = 0.38).

DISCUSSION

Exercise training, as well as a single exercise bout, is able to increase the concentration of circulating progenitor cells, and especially endothelial progenitor cells. Only limited data are available concerning a longer strenuous exercise, like running a marathon or bicycling for a longer time, with respect to the change in EPC concentration and the time-dependent change of the cells during exercise. Therefore the present study was designed to evaluate the effect of 4 h cycling at 70% of IAT on the time-dependent change in circulating progenitor cells.

Our standardized aerobic exercise at 70% IAT for 4 h led to significant changes in the concentration of different blood cells such as leukocytes, lymphocytes, thrombocytes, and monocytes, without a change in lactate levels. Based on these known changes after endurance exercise, two important messages emerged from this study.

1) Hematopoietic (CD34pos or CD133pos) as well as endothelial progenitor cells (CD34pos/KDRpos or CD133pos/KDRpos) exhibited a significant rise after a standardized endurance test. This rise was preceded by a significant elevation of mature endothelial cells (CD146pos) as well as circulating VEGF levels.

2) The detailed investigation of the time frame of cell mobilization during the exercise demonstrated a time-delayed release of circulating progenitor cells with a maximum in most cases at 210 min.

All the observed changes were back to baseline at least 24 h after finishing the exercise.

These results suggest that strenuous exercise at 70% IAT for 4 h leads to a significant rise in progenitor cells (hematopoietic...
and endothelial progenitor cells) potentially due to an elevated level of VEGF and a disturbed endothelial cell layer. This may be regarded as a physiological counteraction to maintain an intact endothelial cell layer.

Influence of Strenuous Activity on Circulating Leukocytes and Thrombocytes

As reported by several authors (21, 34) a significant rise in leukocytes as well as leukocyte subpopulations together with thrombocytes was evident after endurance exercise. The detailed kinetic analysis of the total leukocyte population revealed a biphasic peak, which may be due to a catecholamine followed by cortisol release, as recently described (13). These results clearly demonstrate that the chosen exercise protocol was adequate to induce the well-known cellular responses.

Impact of Strenuous Activity on Mature Endothelial Cells, Microparticles, and Progenitor Cells

Markers of endothelial damage. Circulating endothelial cells (CECs), defined as CD146<sup>pos</sup> cells, are regarded as cellular marker of endothelial damage (19). Increased numbers of CECs have been detected in different conditions associated with vascular damage, like coronary angioplasty for stable angina (6), coronary syndrome (32), and more recently in acute and chronic heart failure (11). In the present study a significant rise of circulating CD146<sup>pos</sup> endothelial cells was observed after 120 min cycling with a maximum after 210 min. What are possible triggers for this increase of mature endothelial cells?

One hypothesis would be that a continuous shear stress of a long period of time leads to a detachment of mature endothelial cells (mECs), but data supporting this idea are not available in the current literature. Other factors discussed to influence the adhesive properties of mECs are proteases and/or cytokines or very simple mechanical injury (19). Nevertheless, additional molecular experiments will be necessary to confirm this mechanism.

Recently, endothelial microparticles (EMPs), defined as CD31<sup>pos</sup>/CD42<sup>neg</sup> microparticles, have been described as another surrogate marker of endothelial damage (35). Elevated EMPs are encountered in patients with acute coronary syndrome, peripheral artery disease, and diabetes mellitus (27, 29).

So far it remains unknown if EMPs derive from resident or circulating endothelial cells. In the present study no change was observed for microparticles and endothelial microparticles. This may be a hint that this type of exercise is not accompanied by a massive irreversible endothelial damage. Nevertheless, we cannot exclude the possibility that we would have seen an exercise-induced change in EMPs, if we would have used another definition like CD31<sup>pos</sup>/CD42<sup>neg</sup> < 1.5 μm (23).

Markers for endothelial repair. With respect to the mobilization of hematopoietic progenitor (CD133<sup>pos</sup> or CD34<sup>pos</sup>) and endothelial progenitor (CD34<sup>pos</sup>/KDR<sup>pos</sup> or CD133<sup>pos</sup>/KDR<sup>pos</sup>) cells, a significant, time-dependent rise was noted after 210 – 240 min. To our knowledge this is the first study investigating this time dependency during strenuous endurance exercise. So far most

![Fig. 5. Quantitative evaluation by flow cytometry of circulating mature endothelial cells identified as CD146<sup>pos</sup> cells (A) and microparticles (MP, ■) as well as endothelial microparticles (EMP, ●) (B) in the blood samples obtained from the participants at the different time points. The values are shown as means ± SE. NS, not significant.](http://jap.physiology.org/)

![Fig. 6. Quantitative evaluation of plasma VEGF (A) and IL-6 concentration (B) in the blood samples obtained from the participants at the different time points. Values are shown as means ± SE.](http://jap.physiology.org/)
of the studies performed a single maximal exercise bout, with the liberalization of the EPCs over time following afterward (1, 39, 46), or they performed and exercise training intervention over a certain time period and determined the training-induced effect on EPC mobilization (26, 30, 31, 37). With respect to the concentration of circulating EPCs, a significant rise at the end of the exercise was seen in this study and a study recently published by Goussietis et al. (22). However, a study recently published by our group on marathon runners could not detect this rise (2). This may be due to an older study population in the marathon study or the different forms of exercise performed (running vs. bicycling).

Taken together, these results suggest that the elevation of these markers describes a clear reaction of the endothelial monolayer. This notion is supported by a recent finding of Dawson and colleagues (12), who reported changes in endothelium dependent vasodilation in the femoral artery after the London marathon. A possible factor responsible for the impairment of vascular function would be an increase of local oxidative stress in the skeletal muscle, which is endorsed by the increase in IL-6, as seen in our study. However, it remains unknown if the increase of EPCs reflects an actual repair of the endothelial cell layer or if it fulfills other tasks.

VEGF as Trigger for the Release of Progenitor Cells

Enforced mobilization of hematopoietic stem cell from the bone marrow has been observed in all species investigated so far, suggesting that similar mechanisms are involved. It appears that during mobilization the bone marrow becomes a playground of a complex interplay between cytokines/chemokines, potent proteases, and adhesion molecules.

Although the understanding of the molecular pathways leading to a mobilization of EPCs from the bone marrow is not fully clear, several studies in the current literature demonstrated that VEGF is one of the most potent molecules triggering an EPC release (4, 28). Mechanistically it is thought that VEGF activates matrix metalloproteinase-9 (MMP-9), which stimulates stem cells to migrate from a quiescent bone marrow niche to the vascular zone (25). That the activation of MMP-9 is a necessary intermediate in the mobilization process is supported by the observation that cytokine-induced progenitor cell mobilization was markedly impaired in MMP-9−/− mice (24). In the present study a temporary significant increase of VEGF was seen, with a maximum occurring after 10 min of exercise. This clearly precedes the rise in circulating progenitor cells. What are possible mechanisms to explain this rapid rise of VEGF? New synthesis via transcription and translation followed by enhanced secretion is out of the question since this process takes at least 4–6 h after the initial stimulus. Another possible explanation would be the secretion of presynthesized VEGF stored in internal vesicles from neutrophils, megakaryocytes, lymphocytes, and macrophages (5, 33, 42). One factor controlling the secretion of VEGF is protein kinase B, also known as Akt (44). In cell culture models a constitutively active form of Akt promoted a VEGF release from coronary artery smooth muscle cells, an effect that was independent of hypoxia-inducible factor HIF-1α. Therefore, one may speculate that exercise induces a currently unidentified signal, which directly or indirectly induces the release of VEGF from internal stores. Nevertheless, this hypothesis requires further intensive investigations.

IL-6, which also showed a time-dependent increase in the present study (maximum at 240 min), plays multiple functions in angiogenesis and vascular remodeling. With respect to its ability to mobilize progenitor cells from the bone marrow, only few data are available. Cesari et al. (9) investigated the amount of circulating EPCs and the concentration of different cytokines, including IL-6. At least in the present study, a significant impact of IL-6 on the mobilization of EPCs can be ruled out, since the time course of elevation is quite similar. Therefore further experiments may be necessary to finally clarify the role of IL-6 as a factor for the mobilization of stem cells.

Limitations

As recently reported, circulating endothelial progenitor cells exhibit a diurnal variation (45). Since we have not included a control group in this study, the exact impact of the exercise session on the variability of the progenitor cells remains unknown. The observed increase in endothelial progenitor cells can be explained mechanistically in two ways: 1) EPCs are directly mobilized from the bone marrow by defined stimuli, or 2) more CD34pos cells start to differentiate into EPCs, thereby increasing their number. Which of the mechanisms is responsible for the observed rise in EPCs in this study cannot be answered by using this study design. Another question that remains unanswered is whether the early increase in VEGF is definitively responsible for the increased mobilization of progenitor cells from the bone marrow. To answer this question a different study design would be necessary. Since all individuals included into this study were well-trained healthy men, it is not clear at the moment if the same effect of strenuous exercise would have been observed in normal but not well-trained men.

Conclusions

The present study demonstrates that strenuous activity in healthy individuals leads to a time-dependent increase of circulating endothelial progenitor cells. This increase may be triggered by a preceding increase in VEGF. Nevertheless, besides these effects also increases in mature endothelial cells as well as the inflammatory marker IL-6 are seen. All these observations suggest that strenuous activity exerts some endothelial damage, which is counteracted by the release of EPCs.

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DISCLOSURES

No conflicts of interest are declared by the authors.

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