A maximal exercise bout increases the number of circulating CD34+/KDR+
endothelial progenitor cells in healthy subjects. Relation with lipid profile

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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 104: 1006–1013, 2008. First published January 24, 2008; doi:10.1152/japplphysiol.01210.2007.—Mobilization of bone marrow-derived endothelial progenitor cells (EPC) might explain exercise-induced improvement of endothelial function. We assessed whether a maximal exercise bout could alter the number of circulating EPC in healthy subjects and whether this effect is related to their cardiovascular risk profile. Additionally, we investigated possible mediators of this effect, namely nitric oxide (NO) bioavailability and vascular endothelial growth factor (VEGF) release. Healthy subjects (group 1, n = 11; group 2, n = 14) performed a symptom-limited cardiopulmonary exercise test on a bicycle ergometer. Numbers of CD34+/kinase insert domain receptor (KDR)+ cells were determined by flow-cytometric analysis, either after magnetic separation of CD34+ cells (group 1) or starting from whole blood (group 2). Serum concentrations of VEGF and NO metabolites were measured by using ELISA. Following exercise, EPC increased by 76% (15.4 ± 10.7 cells/ml vs. 27.2 ± 13.7 cells/ml; P = 0.01) in group 1 and by 69% in group 2 (30.9 ± 14.6 cells/ml vs. 52.5 ± 42.6 cells/ml; P = 0.03). The increase in EPC correlated positively with LDL and total cholesterol/HDL ratio and negatively with peak oxygen consumption and oxygen consumption at anaerobic threshold. VEGF levels increased with exercise, with a strong trend toward significance (P = 0.055). NO levels remained unchanged. The present study demonstrates that a maximal bout of exercise induces a significant shift in CD34+ cells toward CD34+/KDR+ cells. This response was larger in subjects with a less favorable lipid profile.

Subjects

Inclusion criteria for enrolment in this study were nonsmoking, no significant medical history, no active disease nor pharmacological treatment, and no known cardiovascular risk factors. Enrolment took place in May 2005 (group 1, subjects aged between 20 and 30 years; n = 11) and in January 2007 (group 2, subjects aged between 20 and 50 years; n = 14). The study was approved by the local ethical committee, and written informed consent was obtained from all participants.

Study Design

Subjects were asked to refrain from caffeine-containing beverages and excessive physical exertion for 24 h before the study. After an overnight fast, they were called in for a symptom-limited cardiopulmonary exercise test on a graded bicycle ergometer. Immediately before and 10 min after peak exercise, venous blood samples were
drawn from an antecubital vein. The first 3 ml of blood were discarded to prevent contamination with circulating endothelial cells (11).

Cardiopulmonary Exercise Test

Subjects started exercising at a load of 40 Watts, with an incremental load of 20 Watts every minute. Twelve-lead ECG and heart rate were recorded continuously, and automatic cuff blood pressure was measured every 2 min and at peak exercise. Breath-by-breath gas-exchange measurements were performed by using a metabolic cart. Ventilation (V), oxygen uptake (V$\text{O}_2$), and carbon dioxide production (V$\text{CO}_2$) were determined online every 15 s. Peak oxygen consumption (V$\text{O}_2$peak) was determined as the highest attained V$\text{O}_2$ during the final 30 s of exercise and was also expressed as a percentage of the predicted value (V$\text{O}_2$peak%). Subjects were encouraged to exercise until exhaustion, and all of them performed a maximal test according to the identification of the anaerobic threshold (V-slope method) (2).

Laboratory Measurements

**Flow-cytometric analysis of progenitor cells.** Fasting venous blood was collected in acid citrate dextrose tubes and was processed within 4 h of collection. FITC-labeled anti-CD34 and peridinin-chlorophyll protein complex (PerCP)-labeled anti-CD3 were obtained from BD Pharmingen; phycoerythrin (PE)-labeled anti-kinase insert domain receptor (KDR) was from R&D Systems, and incubation was performed following the manufacturer’s instructions. DRAQ5 (Biostatus) was used as a nuclear stain. All samples were pretreated with Fc receptor-blocking reagent (Miltenyi Biotec) for 15 min at room temperature to prevent nonspecific binding of antibodies.

The gating strategy for **group 1** samples was as follows (Fig. 1): peripheral blood mononuclear cells (PBMC) were isolated by density-gradient centrifugation from 40 ml of blood with Lymphosep (MP Biomedicals), and subsequently, CD34+ cells were immunomagnetically separated by using a MiniMacs CD34 separation kit (Miltenyi Biotec). Purity levels ranged from 33.3 to 65%. These CD34+ cells were analyzed for the coexpression of KDR after exclusion of cell aggregates and nonnucleated cells. For the calculation of the absolute number of CD34+/KDR+ cells per milliliter of blood, the content of CD34+ cells in whole, peripheral blood was analyzed by using anti-CD34-FITC antibody. Starting from this number, the absolute number of CD34+/KDR+ cells could be deducted, thereby taking the purity levels of CD34 isolation into account.

For the analysis of the samples of **group 2** (Fig. 2), 200 μl of whole blood was incubated with anti-KDR-PE and anti-CD34-FITC. After lysis of the erythrocytes with a fixative-free erythrocyte lysis reagent containing ammonium chloride solution (StemCell Technologies), the number of CD34+ and CD34+/KDR+ cells were analyzed in the lymphocyte region. Control stainings with isotype-identical antibodies and unstained samples were performed for each sample. Samples were analyzed for a minimum of 500,000 total events on a Coulter Epics XL flow cytometer (Beckman Coulter) and were analyzed with Cytomics RXP software (Beckman Coulter). The percentage of positive cells was converted into absolute numbers of cells per milliliter by using the white blood cell count, and the percentages of lymphocytes and monocytes were obtained from an automated cell counter (ADVIA 2120; Bayer).

The intraobserver reproducibility was excellent for the two methods, with an intraclass correlation coefficient of 0.97 for method 1 and 0.87 for method 2.

**Colony-forming unit assay.** In group 2, PBMC were isolated from 10 ml of peripheral blood and were cultured on fibronectin-coated

![Fig. 1. Gating strategy for group 1 CD34-enriched samples. Firstly, the mononuclear cells are gated in a forward scatter (FS)/side scatter (SS) plot (A). Single cells are selected on a FS area/FS peak plot (B) and nucleated cells by using DRAQ5 (C). Cells positive for CD34 with low side scatter are included (D) and a scatter back-gating is performed that allows exclusion of spurious events (E). Cells double positive for CD34 and kinase insert domain-containing receptor (KDR) expression are analyzed in this cluster (F).](http://jap.physiology.org/content/104/4/1007/F1)

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Fig. 2. Gating strategy for group 2 samples. Lymphocytes are gated in a FS/SS plot (A). A second gate is used to include only those cells positive for CD34 and CD34+/KDR+ cells are determined in this CD34-expressing population (C).

dishes (BD Biosciences) in Endocult liquid medium (StemCell Technologies) at a density of 5 × 10^5 PBMC/well. After 2 days in culture, nonadherent cells were harvested and cultured for an additional 3 days at a density of 1 × 10^6 cells in a fibronectin-coated 24-well culture dish. On day 5 of culture, colonies consisting of a central cluster of round cells and elongating sprouting cells at the periphery were counted manually in a minimum of three wells under an inverted phase-contrast microscope by two independent investigators. Results are expressed as mean colony-forming units (CFU) per well. The intraclass correlation coefficient calculated for the interobserver agreement of CFU count was 0.89, which is evidence of the outstanding agreement between the observers.

Biochemical assays. In both groups, fasting venous blood was collected in serum tubes for measurement of levels of total cholesterol, HDL, and triglycerides. Samples were immediately centrifuged, and serum was stored at −80°C for later analysis.

Measurement of serum VEGF and NO levels. Serum NO metabolites and VEGF levels were assessed in group 2 subjects only. Additionally, 15 healthy individuals, aged 20–50 yr, who fulfilled the inclusion criteria were recruited to evaluate potential exercise-induced changes in NO and VEGF levels. Levels of VEGF were measured by high-sensitivity colorimetric sandwich ELISA (Human VEGF Quantikine ELISA kit; R&D Systems) with a lower detection limit of 0.25 pg/ml. The total NO concentration in serum, prepared by ultrafiltration (14,000 g centrifugation for 30 min using filters with a 10,000 molecular weight cutoff), was measured indirectly by a colorimetric detection of nitrite (NO_2^-) and nitrate (NO_3^-) levels following a nitrate-reduction assay (Total Nitric Oxide and Nitrate/Nitrite Parameter assay kit; R&D Systems) with a lower detection limit of 0.25 μmol/l. This assay determines NO concentrations on the basis of the enzymatic conversion of NO_3^- to NO_2^- by nitrate reductase. The reaction is followed by colorimetric detection of NO_2^- as an azo dye product of the Griess reaction.

Statistics

Analyses were performed in SPSS for Windows version 12.0 (SPSS, Chicago, IL). The normality of continuous data sets was assessed by using one-sample Kolmogorov-Smirnov. Logarithmic transformation was performed where necessary. Continuous data are presented as means ± SD. Paired Student’s t-test and Pearson correlation coefficients were applicable. A P value of <0.05 was considered statistically significant.

RESULTS

Demographic, Biochemical, and Exercise Characteristics

Table 1 summarizes the characteristics of the two study groups. Group 1 and group 2 differed only with regards to mean age (23.9 ± 1.4 vs. 36.2 ± 9.3 yr; P = 0.004) and age

Table 1. Baseline characteristics of study subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>23.9±1.4</td>
<td>36.2±9.3</td>
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<tr>
<td>Male/female, %</td>
<td>55/45</td>
<td>64/36</td>
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<td>Body mass index</td>
<td>21.6±2.5</td>
<td>23.0±3.2</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>115.6±9.5</td>
<td>124.7±11</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>77.6±9.4</td>
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<td>Total cholesterol, mg/dl</td>
<td>183.3±45</td>
<td>184.4±27</td>
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<tr>
<td>LDL, mg/dl</td>
<td>102.2±37.1</td>
<td>114.4±24.3</td>
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<tr>
<td>HDL, mg/dl</td>
<td>67.0±12.8</td>
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<tr>
<td>Total cholesterol/HDL</td>
<td>2.8±0.7</td>
<td>2.7±0.7</td>
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<td>VO_2peak, ml·kg⁻¹·min⁻¹</td>
<td>50.6±10.3</td>
<td>46.0±11.8</td>
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<td>VO_2peak%</td>
<td>116.7±22.2</td>
<td>119.3±23.9</td>
<td>0.9</td>
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<tr>
<td>Maximal load, Watts</td>
<td>255.9±58.3</td>
<td>240.4±58.1</td>
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<td>Percentage predicted load</td>
<td>101.5±10.0</td>
<td>108.5±22.1</td>
<td>0.3</td>
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<tr>
<td>VO_2 at anaerobic threshold, ml·kg⁻¹·min⁻¹</td>
<td>42.0±9.3</td>
<td>36.4±13.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Load at anaerobic threshold, Watts</td>
<td>221.5±51.4</td>
<td>200.7±65.9</td>
<td>0.4</td>
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<td>Exercise training, h/wk</td>
<td>4.1±3.3</td>
<td>3.4±2.2</td>
<td>0.5</td>
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</table>

Values are means ± SD except for male/female ratio; n = number of subjects. VO_2, oxygen consumption; VO_2peak, peak oxygen consumption; VO_2peak%, percentage of predicted peak oxygen consumption.
ACUTE EXERCISE AND ENDOTHELIAL PROGENITOR CELLS

distribution [22–26 vs. 20–48 yr (min-max)]. The values for body mass index (BMI), blood pressure, and lipoproteins confirmed the low cardiovascular risk profile of the studied subjects. Exercise capacity was excellent, as demonstrated by mean values in excess of 100% of predicted for both \( \dot{V}O_2 \)peak and maximal workload in the two groups.

Number of Circulating EPC

In group 1, the absolute number of circulating CD34+/KDR+ cells increased by 76% following a single exercise bout (15.4 ± 10.7 vs. 27.2 ± 13.7 cells/ml; \( P = 0.01 \)). A similar change was detected in group 2, with a 69% increase in CD34+/KDR+ cells (30.9 ± 14.6 vs. 52.5 ± 42.6 cells/ml; \( P = 0.03 \); Fig. 3A). Despite the significant increase in total white blood cell count induced by exercise (Table 2), the increase in CD34+ cells/ml (39% in group 1; 8% in group 2; Fig. 3B) was smaller than the increase in CD34+/KDR+ cells (76% in group 1; 69% in group 2), suggesting a shift in the total CD34+ pool toward CD34+/KDR+ cells.

Relation of Exercise-Induced Increase in EPC

With Cardiovascular Risk Factors

The observed exercise-induced increase in CD34+/KDR+ cells correlated positively with both LDL and total cholesterol/HDL ratio. This finding was consistent in the two study groups (Fig. 4). In group 1, a negative correlation between the increase in CD34+/KDR+ cells and both \( \dot{V}O_2 \)peak and \( \dot{V}O_2 \) at anaerobic threshold was present (Fig. 5). For age, BMI, and systolic and diastolic blood pressure, no significant relations were seen (all \( P > 0.05 \); Table 3).

CFU Assay

The number of CFU was 11.9 ± 10.9 before and 9.0 ± 8.3 after exercise (\( P = 0.2 \)). No significant correlations were found between CFU numbers and exercise or biochemical parameters (all \( P > 0.05 \)).

Serum VEGF and NO Levels

Serum VEGF levels increased with exercise (246.9 ± 142.78 pg/dl before and 262.92 ± 160.0 pg/dl after exercise), with a strong trend toward significance (\( P = 0.055 \)). There was no relation between the increase in VEGF levels and the increase in circulating CD34+/KDR+ cells, cardiovascular risk factors, or exercise capacity (all \( P > 0.05 \)). Serum degradation products of the NO pathway before exercise (47.49 ± 30.85 \( \mu \)mol/l) did not differ from the concentration after exercise (47.85 ± 28.68 \( \mu \)mol/l; \( P > 0.05 \)).

DISCUSSION

The present study was designed to evaluate the effect of a single episode of exercise on the mobilization of CD34+/KDR+ cells in healthy, well-trained individuals with a low cardiovascular risk profile. Several interesting findings emerged from this study.

First, a single maximal exercise bout in healthy subjects elicited a larger increase in CD34+/KDR+ cells than in CD34+ cells, suggesting a shift in circulating CD34+ cells toward CD34+/KDR+ cells. These findings were reproducible in two different cohorts by using two different flow-cytometric techniques. Second, although still within “normal” limits, higher LDL and total cholesterol/HDL levels favored the exercise-induced increase in CD34+/KDR+ cells. Third, the observed increase in VEGF levels underscores its possible role as an EPC-mobilizing factor.

Endothelial Integrity and Repair

Impaired endothelial function precedes the development of overt atherosclerosis and has even been observed in otherwise healthy subjects presenting with a limited coronary risk profile (5, 6). The crucial role of endothelial dysfunction has been exemplified in clinical manifestations of atherosclerosis, such as coronary artery disease, peripheral artery disease, and chronic heart failure (18). Healthy endothelium is capable of translating physical and chemical signals and can provide the necessary adjustment to regulate vascular tone, cellular adhesion, and thromboresistance within normal limits. However, prolonged exposure to cardiovascular risk factors exhausts the protective effect of endothelial cells. The preservation of endothelial integrity depends on the balance between injury and...
the endogenous capacity for repair. Both proliferating mature adjacent endothelial cells and bone marrow-derived EPC are considered key players in endothelial restoration. The latter are released from the bone marrow in response to ischemia or endothelial injury and aim to repair damaged regions, either by producing angiogenic cytokines (17, 25) or by differentiating into endothelial cells (39). The relation between the number and function of circulating EPC and endothelial function has been demonstrated in healthy individuals with a variety of cardiovascular risk factors (15, 37), patients with coronary artery disease (34), PAOD (8), and chronic heart failure (35). Cardioprotective drugs, [i.e., statins (36), angiotensin II receptor antagonists (3), and angiotensin-converting enzyme inhibitors (38)], partly providing benefit through improved endothelial function, have been shown to increase EPC numbers and function.

The Role of Exercise and Physical Training in the Restoration of Endothelial Function

Physical training is a highly effective, multifactorial, non-pharmacological therapeutic approach to treating endothelial dysfunction. Besides its effect on several cardiovascular risk factors, regular exercise is capable of augmenting circulating EPC and of improving their function in different patient populations (16, 22, 29, 31). The underlying mechanism for EPC mobilization is being progressively unraveled. In an animal experiment, Laufs et al. (22) confirmed the central role of NO in the regulation of exercise-induced EPC mobilization. The exercise-induced increase in EPC in eNOS knockout mice was blunted compared with wild-type mice. In addition, the increase in VEGF, seen after physical training, was abolished by cotreatment with \( N^G \)-nitro-L-arginine methyl ester (L-NAME). In patients with PAOD, 4 wk of daily ischemic exercise training led to a significant increase in circulating EPC, which was linearly correlated with the observed changes in VEGF concentration (29). Conversely, coronary artery disease patients participating in an endurance-training program saw both their EPC numbers and endothelial function improved, in relation to increased NO synthesis, but without VEGF alterations (31).

Reports on the effect of a single exercise bout are scarce, and comparison of scientific data is hampered by the absence of standardized protocols for EPC identification and enumeration.
In 25 moderately trained, healthy volunteers, short-term running for 10 min did not augment the number of CD34+/KDR+ cells, whereas intensive and moderate running for 30 min increased CD34+/KDR+ cells significantly (21). In the latter group, CFU numbers were also significantly higher after exercise, without changes in VEGF concentration. In their study including two groups of either young sedentary or trained healthy subjects, Thijssen et al. (33) could not demonstrate an increase in the number of CD34+/KDR+ cells or VEGF concentration immediately after a maximal exercise. Whereas these results clearly contrast with the present data, the baseline absolute number of CD34+/KDR+ in their study population was 10-fold higher, questioning the comparability of either the studied groups or the methods used for flow-cytometric analyses. Circulating EPC, defined as CD133+/vascular endothelial cadherin+ cells, increased fourfold by exercise in middle-aged volunteer subjects characterized by a large variety of cardiovascular risk factors (26). Plasma levels of VEGF and hepatocyte growth factor remained unaltered.

In the present study, we demonstrated that a single maximal exercise bout elicits an increase in CD34+/KDR+ cells and CD34+ cells within just 10 min of exercise. This finding was reproducible in two different populations with the use of two different flow-cytometric techniques. However, the fact that CD34+ increased barely (39% for group 1 and 8% for group 2) compared with CD34+/KDR+ cells (76% for group 1 and 69% for group 2) was remarkable, suggesting a shift in circulating CD34+ cells toward CD34+/KDR+ cells.

Contrary to circulating CD34+/KDR+ EPC, the number of CFU remained unchanged after exercise, and no relation was seen with lipid levels. Although CFU have been related to cardiovascular risk profile and outcome in cardiovascular patients, they have been shown to consist of a mixed population. Recently, evidence was generated that the nature of these cultured cells is different from CD34+/KDR+ EPC per se. They possess myeloid progenitor cell activity, differentiate into phagocytic macrophages, and fail to form vessels in vivo (23, 27, 28, 42).

Despite the fact that real “pathological” tissue ischemia is absent in healthy subjects, pushing themselves to the limits of aerobic capacity during a maximal exercise test will have resulted in a shift to anaerobic glycolytic metabolism, in addition to the generation of oxidative stress. The latter, possibly via increased VEGF levels, might act as a trigger for EPC mobilization. As described by Gavin et al. (10), serum VEGF levels increase directly after exercise and remain elevated for 2 h in healthy subjects. In the present population, the observed increase in VEGF concentration showed a strong trend toward significance. Because there is little data on the time course of serum VEGF regulation following a single bout of exercise, changes in VEGF levels over a larger period of time, particularly in relation to changes in circulating EPC, could provide arguments for a possible paracrine mechanism exerted by EPC and should be studied in future experiments.

Moreover, acute exercise, via higher cardiac output, increases shear stress at the level of the endothelium, which

| Table 3. Relation of exercise-induced increase in endothelial progenitor cells with cardiovascular risk factors |
|---------------------------------|----------------|----------------|----------------|
|                                | Group 1         |                | Group 2         |
|                                | Correlation, r  | P Value        | Correlation, r  | P Value        |
| Age                            | 0.24            | 0.5            | 0.49            | 0.1            |
| Body mass index                | 0.19            | 0.6            | 0.16            | 0.6            |
| Systolic blood pressure        | 0.45            | 0.2            | 0.38            | 0.2            |
| Diastolic blood pressure       | 0.20            | 0.6            | 0.46            | 0.2            |
| Total cholesterol              | 0.53            | 0.09           | 0.43            | 0.1            |
| HDL                            | −0.12           | 0.7            | −0.28           | 0.4            |
| LDL                            | 0.75            | 0.008          | 0.57            | 0.03           |
| Total cholesterol/HDL          | 0.72            | 0.01           | 0.54            | 0.05           |
| V̇O₂peak                       | −0.64           | 0.035          | −0.27           | 0.9            |
| V̇O₂ at anaerobic threshold     | −0.83           | 0.003          | −0.25           | 0.4            |
| Maximal load                   | −0.47           | 0.1            | 0.09            | 0.7            |
subsequently enhances eNOS activity, resulting in EPC mobilization (1). Despite the strong arguments for the role of eNOS upregulation and NO dependency in mediating exercise training-induced EPC liberation (22), we failed to report an increase in NO bioavailability. Possible explanations include the fact that NO levels are assessed indirectly through NO metabolites and that the assay is limited by various interfering preanalytical (e.g., diet, deproteinization of samples) and analytical factors (e.g., contamination of nitrate in chemicals and laboratory ware). However, direct quantification of NO levels requires electron paramagnetic resonance (EPR) spectroscopy, a technique that is not readily available. Secondly, the effect of acute exercise might be short lived, and interference with NO metabolism could well be a paracrine and local endothelial phenomenon.

There is growing evidence for an inverse relation between resting EPC numbers and cardiovascular risk (40). Inverse relations between atherogenic risk factors and circulating EPC have usually been studied at baseline and in patients at risk for cardiovascular disease. The presented results suggest that in healthy individuals, higher lipid levels, conveying a prooxidant vascular environment, provide a stronger EPC-mobilizing stimulus. Although it seems contradictory at first glance, one could hypothesize that exercise in these individuals, characterized by an endothelium “under stress,” might stimulate the generation of reactive oxidant species (ROS), thereby triggering repair mechanisms. ROS production is often evaluated in an indirect manner (12), whereas the optimal technique involves EPR spectroscopy. Future experiments will reveal whether this hypothesis can be confirmed. Of note, Lauer et al. (20) attributed an important eNOS signaling function to exercise-induced endogenous hydrogen peroxide production. In addition, exercise-induced vascular remodeling and enhanced endothelial-dependent vasodilation are limited in time and clearly depend on baseline abnormalities (19). The finding of an inverse relation between maximal and submaximal oxygen consumption and the observed EPC release is concordant with the latter assertion.

Limitations

The present study is limited by the small number of subjects included. However, because there is no consensus nor standard protocol for the quantification of circulating EPC, the fact that our findings were duplicated in a second population using a different flow-cytometric technique is reassuring. A pure methodological comparison of the two techniques, for which a crossover design would have been more appropriate, was beyond the scope of the study.

Secondly, the assessment of changes in EPC function following exercise would have strengthened our message because it has become clear that EPC function is equally important to EPC numbers in vascular homeostasis and angiogenesis (9).

In future studies, it would be interesting to study the time course of EPC mobilization. One could speculate that in the presence of endothelial defects, mobilized EPC are rapidly integrated at sites of injury. Despite the fact that real tissue ischemia is absent in healthy subjects, acute exhaustive exercise might elicit vascular damage and the mobilized EPC might serve to restore vascular integrity.

Conclusions

The present study demonstrates that a single bout of exercise induces a significant shift in circulating CD34+ cells toward CD34+/KDR+ cells in healthy subjects. This response appeared to be larger in subjects with a less favorable lipid profile, which could be a physiological explanation for the well-known benefit of exercise in patients who are prone to develop or already manifest with atherosclerotic disease.

GRANTS

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