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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Submitted 13 November 2007; accepted in final form 24 January 2008

The endothelium has emerged as the key regulator of vascular function. Disturbances in endothelial function precede the development of atherosclerotic lesions and accelerate the occurrence of clinical complications (7). Accumulating evidence indicates that circulating endothelial progenitor cells (EPC) play an important role in the maintenance and repair of the endothelium. These cells are recruited from the bone marrow, circulate in the peripheral blood, and have the capacity to differentiate into mature endothelial cells (39). In patients at cardiovascular risk (40), in those with coronary artery disease (30), and in chronic heart failure patients (35), the number of EPC is reduced. In addition to this quantitative deficit, subnormal function of EPC correlates with impaired endothelial function (14, 41). Conversely, interventions that improve endothelial function, such as physical exercise and statins, apparently have a potent EPC-mobilizing effect and increase their angiogenic capacity (21, 36). Regular physical activity is a central component in the primary and secondary prevention of cardiovascular disease and is associated with reduced morbidity and improved cardiovascular prognosis (24). The benefits of moderate physical activity in both healthy and cardiovascular patients include improved peripheral and coronary endothelial function (6, 13) and collateralization in ischemic heart failure patients (4) and patients with peripheral artery occlusive disease (PAOD) (32).

However, the molecular mechanisms responsible for the beneficial effects of exercise are incompletely understood. The role of endothelial nitric oxide synthase (eNOS) upregulation induced by shear stress, resulting in improved endothelial-dependent vasodilation, has been held largely responsible for the exercise-induced benefits. In addition, the role of nitric oxide (NO) as an EPC-mobilizing factor is being progressively disclosed. In an animal model (22), eNOS dependency of exercise-induced EPC mobilization and improved neoangiogenesis were clearly shown.

The aim of the present study was to assess whether a single bout of exercise can alter the number of circulating EPC in the absence of vascular disease and whether this effect is related to the subject’s lipid profile. Additionally, we looked further into possible mediators of this effect, namely NO bioavailability and the release of VEGF.

METHODS

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 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\textsubscript{O\textsubscript{2}}), and carbon dioxide production (V\textsubscript{CO\textsubscript{2}}) were determined online every 15 s. Peak oxygen consumption (V\textsubscript{O\textsubscript{2peak}}) was determined as the highest attained V\textsubscript{O\textsubscript{2}} during the final 30 s of exercise and was also expressed as a percentage of the predicted value (V\textsubscript{O\textsubscript{2peak}}\% ). 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
dishes (BD Biosciences) in Endocult liquid medium (StemCell Technologies) at a density of 5 × 10⁶ PBMC/well. After 2 days in culture, nonadherent cells were harvested and cultured for an additional 3 days at a density of 1 × 10⁶ 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, collected in serum tubes for measurement of levels of total cholesterol (Total Cholesterol kit; R&D Systems) with a lower detection limit of 0.25 mg/dl. This assay determines NO concentrations on the basis of the enzymatic conversion of NO₃ to NO₂ by nitrate reductase. The reaction is followed by colorimetric detection of NO₂ 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>
<td>0.004</td>
</tr>
<tr>
<td>Male/female, %</td>
<td>55/45</td>
<td>64/36</td>
<td>0.3</td>
</tr>
<tr>
<td>Body mass index</td>
<td>21.6 ± 2.5</td>
<td>23.0 ± 3.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>115.6 ± 9.5</td>
<td>124.7 ± 11</td>
<td>0.3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>77.6 ± 9.4</td>
<td>82.4 ± 11</td>
<td>0.1</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>183.3 ± 45</td>
<td>184.4 ± 27</td>
<td>0.4</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>102.2 ± 37.1</td>
<td>114.4 ± 24.3</td>
<td>0.07</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>67.0 ± 12.8</td>
<td>72.3 ± 15.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>2.8 ± 0.7</td>
<td>2.7 ± 0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>VO₂peak, ml·kg⁻¹·min⁻¹</td>
<td>50.6 ± 10.3</td>
<td>46.0 ± 11.8</td>
<td>0.3</td>
</tr>
<tr>
<td>VO₂peak%,</td>
<td>116.7 ± 22.2</td>
<td>119.3 ± 23.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Maximal load, Watts</td>
<td>255.9 ± 58.3</td>
<td>240.4 ± 58.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Percentage predicted load</td>
<td>101.5 ± 10.0</td>
<td>108.5 ± 22.1</td>
<td>0.3</td>
</tr>
<tr>
<td>VO₂ 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>
</tr>
</tbody>
</table>

Values are means ± SD except for male/female ratio; n = number of subjects. VO₂: oxygen consumption; VO₂peak: peak oxygen consumption; VO₂peak%, percentage of predicted peak oxygen consumption.
Exercise capacity was excellent, as demonstrated by mean values in excess of 100% of predicted for both $\overline{V}_\text{O}_{2\text{peak}}$ 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 total CD34+ cells (15.4 ± 10.7 vs. 11.7 ± 7.8 cells/ml; $P = 0.03$) 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 $\overline{V}_\text{O}_{2\text{peak}}$ and VO2 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 μmol/l) did not differ from the concentration after exercise (47.85 ± 28.68 μmol/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 higher 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 \( \text{N}^\text{G}-\text{nitro-L-arginine methyl ester (L-NAME)} \). 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+ cells 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**

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>P Value</th>
<th>Group 2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.24</td>
<td>0.5</td>
<td>0.49</td>
<td>0.1</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.19</td>
<td>0.6</td>
<td>0.16</td>
<td>0.6</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.45</td>
<td>0.2</td>
<td>0.38</td>
<td>0.2</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.20</td>
<td>0.6</td>
<td>0.46</td>
<td>0.2</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.53</td>
<td>0.09</td>
<td>0.43</td>
<td>0.1</td>
</tr>
<tr>
<td>HDL</td>
<td>−0.12</td>
<td>0.7</td>
<td>−0.28</td>
<td>0.4</td>
</tr>
<tr>
<td>LDL</td>
<td>0.75</td>
<td>0.008</td>
<td>0.57</td>
<td>0.03</td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>0.72</td>
<td>0.01</td>
<td>0.54</td>
<td>0.05</td>
</tr>
<tr>
<td>VO2_peak</td>
<td>−0.64</td>
<td>0.035</td>
<td>−0.27</td>
<td>0.9</td>
</tr>
<tr>
<td>VO2 at anaerobic threshold</td>
<td>−0.83</td>
<td>0.003</td>
<td>−0.25</td>
<td>0.4</td>
</tr>
<tr>
<td>Maximal load</td>
<td>−0.47</td>
<td>0.1</td>
<td>0.09</td>
<td>0.7</td>
</tr>
</tbody>
</table>
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, Bauer 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

E. Van Craenenbroeck is supported by a Ph.D. fellowship grant from the Fund for Scientific Research, Flanders, Belgium (FWO-Vlaanderen).

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