IT IS WELL ESTABLISHED THAT lifestyle changes play a major role in secondary prevention after myocardial infarction (12, 24). Therefore, patients get the advice to take part in cardiac rehabilitation programs, which are intended to prevent reinfarction occurrence through a combination of pharmacological intervention and a healthy lifestyle. Besides diet/nutritional counseling, weight control management, lipid management, blood pressure monitoring, smoking cessation, and psychosocial management, physical activity and physical exercise are central recommendations of secondary prevention programs (28).

Regarding physical activity, multiple studies demonstrated an inverse correlation with coronary risk factors. Consequently, it contributes to primary as well as secondary prevention (28, 35). One important mechanism by which physical activity confers protection is the preservation or even improvement of endothelial integrity and, as a consequence, vascular function. In this context, it was repeatedly shown that exercise increased a shear stress-mediated elevation of nitric oxide bioavailability (2). Furthermore, there is accumulating evidence that the exercise-induced mobilization of CD34+/kinase insert domain receptor (KDR+) and CD45+/CD34+ cells may play a role in maintaining endothelial integrity and function, as well as in postnatal neovascularization (13, 29, 32). CD34+/KDR+ cells are considered to be a bone marrow-derived subpopulation of the hematopoietic stem cell fraction that coexpress vascular endothelial growth factor receptor type-2/KDR. These cells are often referred to as endothelial progenitor cells (EPCs) (4, 7). Alternatively, CD34+/KDR+ cells may represent mature endothelial cells (8). EPCs are known to improve the balance between endothelial injury and recovery, since resident vascular endothelial cells possess only limited regenerative potential (19). CD45+/CD34+ are regarded as hematopoietic progenitor cells (HPCs). Whether HPCs significantly contribute to (cardio)vascular regeneration at all, as well as potential mechanisms underlying putative regenerative effects, is still controversial. Regarding the latter, transdifferentiation (19, 32) and paracrine effects of HPCs (17, 23) are discussed. Accordingly, the inclusion of HPCs in future studies related to (cardio)vascular regeneration should be instrumental to eventually elucidate their role.

Reduced functionality (e.g., clonogenic activity, migration) and counts of peripheral CD34+/KDR+ were found to be associated with major cardiovascular risk factors in healthy people, as well as in patients with coronary artery disease (CAD) (7, 36). Furthermore, the number and functionality of CD34+/KDR+ cells seem to correlate with endothelial function and, accordingly, appear to be predictive for the patient’s combined Framingham risk factor score (36).

Several forms of exercise have been reported to improve number and functions of EPCs and HPCs in healthy subjects, as well as in patients with CAD. It was demonstrated that moderate and intensive bouts of acute exercise mobilized both HPCs as well as EPCs into the blood (1, 21, 33). Furthermore, cell numbers as well as clonogenic activity of progenitor cells seem to be affected by regular exercise training. It is assumed that increased HPC levels reflect an adaptation response to habitual exercise training (5, 15). Accordingly, mobilization

Activity of daily living is associated with circulating CD34+/KDR+ cells and granulocyte colony-stimulating factor levels in patients after myocardial infarction

Karsten Krüger, Rainer Klocke, Julia Kloster, Sigrid Nikol, Johannes Waltenberger, and Frank C. Mooren

1Department of Sports Medicine, Institute of Sports Sciences, Justus-Liebig-University, Giessen, Germany; and 2Department of Cardiovascular Medicine, University of Münster, Münster, Germany

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Krüger K, Klocke R, Kloster J, Nikol S, Waltenberger J, Mooren FC. Activity of daily living is associated with circulating CD34+/KDR+ cells and granulocyte colony-stimulating factor levels in patients after myocardial infarction. J Appl Physiol 116: 532–537, 2014. First published January 9, 2014; doi:10.1152/japplphysiol.01254.2013.—The study aimed to investigate whether the extent of activities of daily living (ADL) of patients after myocardial infarction affect numbers of circulating CD34+/KDR+ and CD45+/CD34+ cells, which are supposed to protect structural and functional endothelial integrity. In a cross-sectional study, 34 male coronary artery disease patients with a history of myocardial infarction were assessed for times spent per week for specific physical ADL, including basic activities (instrumental ADL), leisure time activities, and sport activities, using a validated questionnaire. Individual specific activity times were multiplied with respective specific metabolic equivalent scores to obtain levels of specific activities. Numbers of circulating CD34+/KDR+ and CD45+/CD34+ cells were analyzed by flow cytometry. Furthermore, the colony-forming capacity of CD34+ cells and the level of granulocyte colony-stimulating factor (G-CSF) in serum were measured. Analysis revealed that the extent of total activities and basic activities, as well as total activity time, were positively correlated with numbers of circulating CD34+/KDR+ cells (r = 0.60, 0.56, and 0.55, P < 0.05). Higher levels of total activity were also associated with increased colony-forming capacity of CD34+ cells (r = 0.54, P < 0.05) and with higher systemic levels of G-CSF (r = 0.44, P < 0.05). These findings indicate that even ADL-related activities of coronary artery disease patients after myocardial infarction exert stimulating effects on CD34+/KDR+ cell mobilization, potentially mediated by increased G-CSF levels. This, in turn, potentially contributes to the beneficial effects of exercise on the diseased cardiovascular system.
and functional improvement of these cells might represent an additional important beneficial outcome of exercise training. The quantity and intensity of physical activity required for an effective prevention of coronary heart disease (CHD) is still controversial. In this regard, it was demonstrated that, besides controlled regular sport activities, a high level of activity of daily living (ADL) also reduced cardiovascular risk in primary as well as in secondary prevention (31). However, up until now, it is not clear whether CD34+/KDR+ or CD45+/CD34+ cells contribute to the positive effects of ADL.

Therefore, the primary objective of the present study was to examine whether ADL is associated with increased numbers or function of CD34+/KDR+ and CD45+/CD34+ cells in CAD patients with a history of myocardial infarction. As we hypothesized, it was found that patients with a high activity level have higher numbers of circulating progenitor cells with increased clonogenic activity. We additionally analyzed blood levels of the hematopoietic cytokine granulocyte colony-stimulating factor (G-CSF) since it might be a mediator of increased CD34+/KDR+ and CD45+/CD34+ cell mobilization (11, 26).

METHODS

Study population. Thirty-four male CAD patients were included in the study. All patients had a history of myocardial infarction 2–5 yr previously and attended an ambulant cardiac rehabilitation program usually one or two times a week for ~60 min each session. Their average age was 68.3 ± 7.8 yr, and all patients (34 of 34, 100%) had hypertension and hypercholesterolemia. The prevalence of diabetes was 24% (8 patients). All patients were nonsmokers and treated according to the guidelines of the German Cardiac Society. Accordingly, all included patients were treated with β-blockers, statins, angiotensin I-converting enzyme inhibitors and acetylsalicylic acid. Exclusion criteria were left ventricular ejection fraction <30%, age <75 yr, and presence of any medical condition that makes exercise unsafe [unstable angina, sustained ventricular arrhythmias, diagnosis of chronic obstructive pulmonary disease (Guidelines for the Diagnosis and Therapy of COPD Issued by the Deutsche Atemwegsliga), uncontrollable arterial hypertension, diabetes, and hyperthyroidism], or any functional condition that limits physical activity. Informed consent was obtained from all subjects. The Local Ethical Committee of the Justus-Liebig-University Giessen (Germany) approved the study, according to the declaration of Helsinki.

Assessment of physical activity. To quantify the extent of various subtypes of physical activities per week (expressed as average total energy expenditure by physical activity per week), a validated questionnaire was used. The questionnaire encompasses questions on basic activities (instrumental activities of daily living, e.g., walking, cycling to work, stair walking), as well as on leisure time activities (e.g., gardening, etc.), and on sport activities (e.g., Nordic walking, swimming, tennis) (German version of “Compendium of physical activities”) (3, 10). The hours spent on the various subtypes of activities in a week were multiplied with their respective specific metabolic equivalent (MET) score, to obtain activity values. Individual values were given as MET hours per week, with highest values indicating highest activity. The sum of MET hours per week of all subtypes of activities of a subject is designated as his total activity. The reliability of the questionnaire was controlled using the Digi-Walker step counter (38). A significant correlation between steps per week and total activity was found (r = 0.65, P < 0.05).

Blood collection and flow cytometric analysis. Venous blood samples were taken in the morning between 8–9 AM after an overnight fasting. Blood was collected in plastic tubes anticoagulated with EDTA for cell isolation and without anticoagulants for sera cytokine analysis. The sera samples without anticoagulants were centrifuged at 2,000 g for 15 min and then stored in aliquots at ~80°C for further cytokine analysis.

CD45+/CD34+ and CD34+/KDR+ cell numbers were determined after erythrocyte lysis and isolation of whole leukocyte fraction by flow cytometry (Beckmann Coulter, EPICS XL, Krefeld, Germany). Numbers of isolated leukocytes were determined using a Sysmex automated cell counter. For analysis of CD45+/CD34+ number, cells were detected with fluorescent dye-coupled monoclonal antibodies against CD45 (PC-5, Beckman Coulter) and CD34 (FITC, ImmunoTools, Friesoythe, Germany). For analysis of CD34+/KDR+, cells were detected with fluorescently labeled monoclonal antibodies against CD45, CD34, and KDR (CD309) (PE, Beckman Coulter). CD34+/KDR+ cells were defined as being negative for CD45 and positive for CD34, as well as for KDR. The absolute numbers of CD34+/KDR+ cells and CD45+/CD34+ were calculated by using cell counts and percentage portions from flow cytometric analysis.

Colonoid-forming capacity. CD34+ cells were isolated by using a human whole blood CD34+ selection kit (Stem Cell Technologies, Vancouver, BC, Canada), according to the manufacturer’s protocol. Briefly, EasySep Positive Selection Cocktail was added to leukocytes suspension and incubated at room temperature for 15 min. EasySep Magnetic Nanoparticles were added and incubated at room temperature for another 10 min. Positive selection was performed by using a magnetic field, which held the magnetically labeled cells inside the tube, while the supernatant fraction was repeatedly poured off. After determination of the number of isolated cells by using an automated cell counter, cells were plated in 1.1-ml methylcellulose medium (Methocult, Stem Cell Technologies) for 12 days and placed at 37°C in a humidified chamber with 5% CO2. Colonies containing at least 30 cells were scored by light microscopy (Leica DMI 6000B, Wetzlar, Germany). Numbers of colonies were analyzed as colony-forming capacity (CFC) in relation to numbers of cultured CD34+ cells.

Biochemistry. For the quantitative detection of G-CSF in serum samples, a commercially available ELISA (Human G-CSF Quantikine HS ELISA, catalog no. HSTCS0) was used according to the manufacturer (R&D Systems, Minneapolis, MN) protocol. High-sensitive C-reactive protein (CRP) was measured by immunoturbidimetric assay (Beckman Coulter).

Statistical analysis. Data are presented as means ± SD. For statistical analysis, we calculated several correlation analyses to identify the potential influence of activity on cell numbers and function. More precisely, we correlated CD45+/CD34+ and CD34+/KDR+ cell numbers, CFCs, and G-CSF levels with total activities, basic activities, leisure time activities, sport activities, and activity time. We further correlated CD45+/CD34+ with G-CSF levels. In all cases, correlation analyses were performed using the Pearson correlation coefficient.

To determine the possible influence of other confounding factors on numbers of CD34+/KDR+ cells, a multiple-regression analysis was performed. Here, the variables age, body mass index (BMI), and low-density lipoprotein were stepwise added to the multiple linear regression analysis. Statistical significance was assumed when a null hypothesis could be rejected at P < 0.05. Statistical analysis was performed using SPSS 11.5 for Windows. Data analysis was performed by SPSS version 20 (IBM SPSS Statistics 20, IBM, Munich, Germany).

RESULTS

Baseline characteristics. Detailed patient characteristics are depicted in Table 1. The mean values ± SD of numbers of CD34+/KDR+ and CD45+/CD34+ cells, colony-forming units, inflammation markers, cytokine concentration, and of physical activity levels of study participants are summarized in Table 2.
Table 1. Demographic and clinical information for study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>68.3 ± 7.8</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>85.3 ± 11.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1 ± 4.3</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>47.5 ± 9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>61.5 ± 6.1</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>132 ± 12</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>84 ± 7</td>
</tr>
<tr>
<td>Uric acid, mg/dl</td>
<td>5.8 ± 1.2</td>
</tr>
<tr>
<td>Urea, mg/dl</td>
<td>46.1 ± 12.0</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>183.3 ± 38.3</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>51.6 ± 11.5</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>113.3 ± 35.3</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>145.9 ± 72.2</td>
</tr>
</tbody>
</table>

SD, standard deviation; LVEF, left ventricular ejection fraction; mg/dl, miligrams per deciliter; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

Association between CD34+/KDR+ cells, colony-forming capacity, and physical activity. At first, the relationship between progenitor cell numbers and physical activity was analyzed. Calculations revealed that CD34+/KDR+ cells were positively associated with total activity ($r = 0.60$, $P = 0.023$) (Fig. 1A). Further analysis of physical activity subscores demonstrated a significant association between CD34+/KDR+ cells and basic activities ($r = 0.56$, $P = 0.021$) (Fig. 1B). When calculating number of CD34+/KDR+ cells and total activity time, a significant positive association was found ($r = 0.55$, $P = 0.031$) (Fig. 1C). In a second step, a multiple regression analysis was calculated to control for possible confounding factors. This analysis revealed no significant influence of the variables age, BMI, and lipid status. The standardized regression coefficients for the full model were as follows: CD34+/KDR+ cells and total activity $\beta = 0.62$, CD34+/KDR+ cells and basic activities $\beta = 0.51$, CD34+/KDR+ cells and total activity time $\beta = 0.54$. Associations between number of CD34+/KDR+ cells on the one hand and leisure time activities and sport activities on the other were also positive but are characterized by lower coefficients of correlation ($r = 0.42$ ($P = 0.048$) and $r = 0.41$ ($P = 0.05$)). Regarding CD45+/CD34− cells, no association to any kind of physical activity was found. Next, the clonogenic capacity of CD34+ cells was investigated. Similar to the CD34+/KDR+ cell numbers, there was a significant positive association between colony-forming capacity and total physical activity ($r = 0.54$, $P = 0.005$, Fig. 2) and colony-forming capacity and basic activities ($r = 0.51$, $P < 0.023$, not shown). The standardized regression coefficients for the full model were $\beta = 0.52$ for colony-forming capacity and total physical activity and $\beta = 0.49$ for colony-forming capacity and basic activities. In contrast, no significant associations were found between number of colony-forming capacity and activity time or sport activities (not shown). There

Table 2. Number of circulating cells (CD34+/KDR+ and CD45+/CD34+), colony-forming concentration, and physical activity of study participants

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean ± SD</th>
</tr>
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<tbody>
<tr>
<td>Circulating cells</td>
<td></td>
</tr>
<tr>
<td>CD45+/CD34+, cells/ml</td>
<td>8,244 ± 3,240</td>
</tr>
<tr>
<td>CD34+/KDR+, cells/ml</td>
<td>460 ± 391</td>
</tr>
<tr>
<td>Colony-forming capacity</td>
<td></td>
</tr>
<tr>
<td>Colonies, no/cultured CD34+ cells, $\times 10^{-3}$</td>
<td>2.7 ± 1.2</td>
</tr>
<tr>
<td>Inflammatory status</td>
<td></td>
</tr>
<tr>
<td>Leukocytes, $\times 10^{9}$/ml</td>
<td>6.0 ± 1.0</td>
</tr>
<tr>
<td>hsCRP, μg/ml</td>
<td>1.4 ± 0.8</td>
</tr>
<tr>
<td>Cytokine</td>
<td></td>
</tr>
<tr>
<td>G-CSF, pg/ml</td>
<td>18.8 ± 9.1</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
</tr>
<tr>
<td>Total activity, MET h/wk</td>
<td>50.5 ± 27.3</td>
</tr>
<tr>
<td>Sport activity, MET h/wk</td>
<td>15.6 ± 10.2</td>
</tr>
<tr>
<td>Leisure time activity, MET h/wk</td>
<td>11.2 ± 7.6</td>
</tr>
<tr>
<td>Basic activity, MET h/wk</td>
<td>24.5 ± 16.1</td>
</tr>
<tr>
<td>Total activity time, h/wk</td>
<td>12.9 ± 7.3</td>
</tr>
</tbody>
</table>

KDR+, kinase insert domain receptor; hsCRP, high-sensitive C-reactive protein; G-CSF, granulocyte colony-stimulating factor; MET, metabolic equivalent.

Fig. 1. Relation of CD34+/KDR+ cells with levels of total activity (A), basic activities (B), and activity time (C) are shown. MET, metabolic equivalent.
were also no associations between CD34+/KDR+ cells and inflammatory markers, anthropometric data, or clinical data.

**Association between CD34+/KDR+ cells, G-CSF levels, and physical activity.** Correlation analysis revealed that there was a positive association between numbers of CD34+/KDR+ cells and G-CSF levels (r = 0.54, P = 0.005) (Fig. 3A). Furthermore, there was a positive correlation between G-CSF levels and level of total physical activity (r = 0.44, P = 0.048) (Fig. 3B), as well as for G-CSF levels and basic activities (r = 0.48, P = 0.041, data not shown). Standardized regression coefficients for the full model were as follows: CD34+/KDR+ cells and G-CSF levels β = 0.52, G-CSF levels and level of total physical activity β = 0.41, and G-CSF levels and basic activities β = 0.50. In contrast, there were no associations for G-CSF and sport activities or G-CSF and activity time, respectively. Similarly, there were no associations between G-CSF levels and colony-forming capacity.

**DISCUSSION**

The present cross-sectional study revealed that numbers of CD34+/KDR+ cells in blood of CAD patients were positively associated with total physical activity and basic activities of daily living. Furthermore, total activity was positively associated with the CFC of progenitor cells. As a potential mediator of increased counts of CD34+/KDR+ cells, the hematopoietic cytokine G-CSF was identified, since total physical activity and numbers of CD34+/KDR+ cells were also associated with higher levels of systemic G-CSF. Linear regression analysis suggests that these findings are independent of age, BMI, inflammatory markers, or anthropometric or clinical data.

Over the last years, several basic as well as applied research studies demonstrated a beneficial effect of circulating CD34+/KDR+ cells on endothelial function. In this context, EPCs have been shown to be important for the restoration of injured endothelium. Accordingly, it can be assumed that higher numbers of CD34+/KDR+ cells in blood increase the potential for endothelial recovery (2). However, absolute cell numbers of EPCs and HPCs vary between different studies, and information about the ranges of normal values are still limited as different markers are used for the identification and quantification of absolute numbers of circulating EPCs (14). The use of the combinations of the markers CD45 and CD34 as well as CD34 and KDR are common for the detection of HPCs or EPCs, respectively (38). Accordingly, total numbers of CD34+/KDR+ and CD45+/CD34+ cells detected in the present study are similar to those detected in previous studies using the same markers (25, 33).

**Factors affecting numbers of CD34+/KDR+ cells.** Currently, several factors have been reported to affect the number and function of EPCs. Decreased levels have been found with increasing age, smoking, and disease states like diabetes, hypertension, hypercholesterolemia, and obesity (13, 36). In contrast, some pharmacological agents like statins and erythropoietin have been found to increase progenitor cells (2). Actually, several studies reported positive effects of physical exercise on EPC and HPC numbers and function in both patients with vascular disease, as well as healthy subjects, suggesting that this effect is one of those underlying the beneficial outcomes of physical exercise (34, 39). Both acute exercise, irrespective of whether of moderate or high intensity, as well as regular exercise training, were followed by increased numbers of progenitor cells in peripheral blood of both healthy subjects as well as patients with cardiovascular disease (18, 20). Thereby mobilization during training periods seemed to be time dependent, needing a minimum of 28 days (20, 30). A limitation of these training studies was that, despite controlled exercise training programs, patients, as well as healthy sub-

![Fig. 2. Relation of colony-forming capacity with physical activity level. Positive association of number of colonies derived from CD34+ cells and level of total activity is shown.](http://jap.physiology.org/)

![Fig. 3. Relation between CD34+/KDR+ cells, granulocyte colony-stimulating factor (G-CSF) levels, and physical activity. A positive association was found for CD34+/KDR+ cells and peripheral G-CSF levels (A) and G-CSF levels and total physical activity (B).](http://jap.physiology.org/)
jects, exhibit a great variety of basic and leisure time physical activity (10). Current data indicate that these low-intensity activities also affect cell mobilization. Therefore, in the present study, a physical activity questionnaire was used that assessed total physical activity and subscores like sport activities, as well as basic and leisure time activities. A limitation of the method might be the self-assessment of activity. However, the use of technical tools for measuring physical activities, like step counter or accelerometer, due to their inherently limited range of applicability, do not allow for the reliable assessment of total physical activities (22).

It is well known that a large proportion of individuals in the Western World remain inactive. The reasons for the lack of participating in physical activity programs or sport activities are manifold and range from lack of motivation to cardiovascular or musculoskeletal impairment, especially in older people (16). Therefore, an instrumental strategy to improve the activity level is to increase energy expenditure through movements embedded in routines of daily live (e.g., gardening, taking the stairs). Data from the Harvard Alumni study demonstrated that total physical activity showed similar reductions in CHD risk, like regular participation in vigorous activities (31). Current results suggest that an increase of CD34+/KDR+ cells could be a potential mechanism underlying reduction of CHD risk by physical activity. Accordingly, patients with cardiovascular disease should not only take part in controlled exercise programs at specific intensities, but also should try to achieve physical activity. The activity-dependent increase of CD34+ cells active healthy subjects and patients might also be the result of decreased senescence and apoptosis, or increased CFC (2, 36). Similar effects on clonogenic activity of CD34+ cells were previously demonstrated for healthy middle-aged and aged men who took part in regular endurance exercise (15). In this context, it was also reported that clonogenic activity might be a better predictor of endothelial dysfunction than conventional risk factors in this population (7, 15). Therefore, current results extend this knowledge that also ADL induces functional changes in these cells.

Currently, it can only be speculated about the mechanisms causing the increase of CD34+/KDR+ cell numbers secondary to exercise and all day activities. The activity-dependent increase of G-CSF concentration, which we have shown in the present work, supports the notion that increased cell numbers were the result of an increased mobilization from bone marrow, as G-CSF is probably the most potent progenitor cell mobilizing cytokine (11). In agreement with other studies, it could be also demonstrated that it is one of several cytokines that responds to exercise (26). A correlation to ADL in healthy older subjects was demonstrated previously by our group (9). However, G-CSF-related beneficial effects of ADL could also or additionally be due to direct influences (e.g., inhibition of cell death and stimulation of proliferation) of the cytokine on various cell types of the cardiovascular system, including endothelial cells, vascular smooth muscle cells, and cardiomyocytes (11).

The beneficial effect of ADL could also be caused by its well known anti-inflammatory effects (27). In this context, it was repeatedly shown that regular exercise reduced CRP levels in patients with cardiovascular diseases (37). Despite some known interactions between inflammatory mediators and CD34+/KDR+ cells (6), an association neither between CRP levels and physical activity, nor between CRP levels and CD34+/KDR+ cell counts was found. The absence of associations with cell numbers and CRP could be because of the rather low and limited range of CRP values in this subject cohort.

In conclusion, increased circulating CD34+/KDR+ cell numbers and clonogenic activity seemed to be associated with activities of daily living in patients with a history of myocardial infarction. These findings strengthen the recommendation not only to take part in controlled exercise programs in secondary prevention, but also to increase basic activities and activity times. In accordance with the available literature, our findings support the role of CD34+/KDR+ cells as important mediators of the supportive effect of physical activity on vascular functionality in cardiovascular disease.

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