Level and Value of Circulating Endothelial Progenitor Cells in Patients After Acute Ischemic Stroke

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Background and Purpose—Endothelial progenitor cells (EPCs) migrate from bone marrow to systemic circulation in response to tissue ischemia where they differentiate into mature endothelial cells for angiogenesis in situ. This study tested the hypothesis that the level of circulating EPCs is substantially increased and predictive of prognostic outcomes after acute ischemic stroke (IS).

Methods—The level of circulating EPCs (staining markers: CD31/CD34 [E1], CD62E/CD34 [E2], and KDR/CD34 [E3]) were examined using flow cytometry at 48 hours after acute IS in 138 consecutive patients. The EPC level was also evaluated once in 20 healthy volunteers and in 40 at-risk control subjects.

Results—Level of circulating EPCs (E1–3) was significantly higher in patients with IS than in at-risk control subjects (P<0.05). Additionally, EPC (E1–3) level was significantly lower in patients with severe neurological impairment (defined as a score ≥12 on the National Institutes of Health Stroke Scale) than in patients with less severe impairment (National Institutes of Health Stroke Scale < score 12) at 48 hours after IS (P<0.0001). Moreover, the EPC (E3) level was strongly correlated with improved National Institutes of Health Stroke Scale ≥4 on day 21 after IS (P=0.0004). Furthermore, low circulating EPC level was independently predictive of severe neurological impairment (National Institutes of Health Stroke Scale ≥12) at 48 hours (E1–3) and combined major adverse clinical outcomes (defined as recurrent IS, any cause of death, or National Institutes of Health Stroke Scale of ≥12) on day 90 (E1–3) after IS (P<0.001).

Conclusions—Level of circulating EPCs is independently predictive of prognosis after IS. (Stroke. 2008;39:69-74.)

Key Words: circulating endothelial progenitor cells ■ ischemic ■ neurological impairment ■ stroke

Stroke, a growing epidemic, is an important cause of mortality and disability worldwide.6 Severity of motor deficit at the acute phase, an index of brain infarction/ischemia but not age or gender, is independently predictive of future clinical outcomes after ischemic stroke.2

Coronary artery disease and cerebrovascular disease, which comprise the majority of the same causal etiologies resulting in endothelial damage and arteriosclerosis, constitute arterial obstructive syndromes. Thus, coronary artery disease and cerebrovascular disease are 2 sides of the same coin. Surprisingly, although both ischemic preconditioning and development of collaterals are known to reduce myocardial damage after acute myocardial infarction,4–5 no data are available regarding these mechanistic basis of protection from reducing brain ischemia after acute ischemic stroke (IS). Interestingly, studies have demonstrated that the formation of collaterals after myocardial ischemia results from migratory activity of endothelial progenitor cells (EPCs).6

The bone marrow contains different types of stem cells. The CD34
cells, nonhematopoietic stem cells in humans, released from bone marrow to circulation are known as circulating bone marrow-derived EPCs; these EPCs incorporate into newly formed blood vessels and augment neovascularization.3 In addition, bone marrow-derived EPCs have been found to play a major role in angiogenesis and regeneration of ischemic cardiovascular tissue based on human and animal model studies.8–9 However, no study has addressed the role of circulating EPCs on clinical outcome after IS. Accordingly, this study tested the hypothesis that significantly increased level of circulating EPCs is a reliable indicator of prognosis after acute IS.

Materials and Methods

Study Patients
This study included consecutively admitted patients with acute IS at a single facility between November 2005 and October 2006. An

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estimated sample size of 150 patients was based on the effective size with an α = 0.05, a power of 80%, a difference in circulating level of EPCs between the study and normal volunteers of 1.0%, and a standard deviation of 1.0% in at-risk control subjects and 2.0% in study patients. A 20% rate of protocol violations and incomplete follow-up was assumed. Stroke was defined as sudden onset of loss of global or focal cerebral function persisting for more than 24 hours. Patients with any history of the following were excluded from the study: intracranial hemorrhage, surgery or trauma within the preceding 3 months, abnormal liver function, hematologic disorders, renal insufficiency (creatinine >1.5 mg/dL), malignancy, febrile disorders, acute or chronic inflammatory disease at study entry, atrial fibrillation, or congestive heart failure. Over a period of 10 months, 156 consecutive patients with IS occurring less than 72 hours before evaluation were included. Eighteen (11.5%) of the 156 patients were excluded due to subsequent fever and sepsis (6 patients), unavailable MRI data (2 patients), intracranial hemorrhage (2 patients), paroxysmal atrial fibrillation (4 patients), or incomplete follow-up (4 patients) that occurred later after the IS. Therefore, the remaining 138 patients constituted the study population.

Risk factor controls included 40 subjects matched by age, gender, hypertension, diabetes mellitus, current smoking, and hypercholesterolemia. Twenty age-matched and gender-matched healthy volunteers were also studied. Informed consent was obtained from all study subjects. The study protocol was approved by the Institutional Review Committee on Human Research in our institution.

### Neurological Assessment

Evaluation of physical function and neurological impairment of stroke patients was based on the National Institutes of Health Stroke Scale (NIHSS) during the acute, convalescence (on day 21), and chronic (day 90) phases of stroke. Severe neurological impairment (alive in care) was defined as a score of ≥12 on the NIHSS based on a previous reported study. This model gave a sensitivity of 0.76 and a specificity of 0.89 at 30-day follow-up. Thus, patients with IS with NIHSS ≥12 were categorized into group 1 and those with NIHSS <12 (defined as having less severe neurological impairment) were categorized into group 2.

### Imaging Studies and Laboratory Investigations

In addition to full clinical assessment, ancillary examinations were performed, including white blood cell count, biochemical data, chest x-ray film, routine brain CT and MRI/magnetic resonance angiography, duplex scanning of the carotid arteries, and routine cardiac analysis by of 12-lead electrocardiography and echocardiography.

### Blood Sampling and Assessment of Circulating Endothelial Progenitor Cell Level by Flow Cytometry

Blood samples were obtained once at 48 hours after IS at 9:00 AM. Ten milliliters of blood was drawn from the antecubital vein into a Vacutainer containing 3.8% buffered sodium heparin. Blood samples were also obtained in both control subjects once at the acute, chronic (day 90) phases of stroke. Severe neurological impairment (alive in care) was defined as a score of ≥12 on the NIHSS based on a previous reported study. This model gave a sensitivity of 0.76 and a specificity of 0.89 at 30-day follow-up. Thus, patients with IS with NIHSS ≥12 were categorized into group 1 and those with NIHSS <12 (defined as having less severe neurological impairment) were categorized into group 2.

### Table 1. Baseline Characteristics of Stroke, At-Risk Control, and Normal Control Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study Patients (n=138)</th>
<th>At-Risk Control (n=40)</th>
<th>Normal Control (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>66.3±10.4</td>
<td>66.5±9.5</td>
<td>67.1±9.3</td>
<td>0.945</td>
</tr>
<tr>
<td>Male, % (n)</td>
<td>65.9% (91)</td>
<td>62.5% (25)</td>
<td>60.0% (12)</td>
<td>0.831</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>71.7% (99)</td>
<td>67.5% (27)</td>
<td>...</td>
<td>0.604</td>
</tr>
<tr>
<td>Diabetes mellitus, % (n)</td>
<td>42.0% (58)</td>
<td>40.0% (16)</td>
<td>...</td>
<td>0.819</td>
</tr>
<tr>
<td>Current smoking, % (n)</td>
<td>26.5% (36)</td>
<td>32.5% (13)</td>
<td>...</td>
<td>0.424</td>
</tr>
<tr>
<td>Hypercholesterolemia, % (n)</td>
<td>47.1% (65)</td>
<td>50.0% (20)</td>
<td>...</td>
<td>0.474</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.8±2.8†</td>
<td>24.5±2.7†</td>
<td>22.8±2.0†</td>
<td>0.008</td>
</tr>
<tr>
<td>Previous stroke by history, % (n)</td>
<td>37.0% (51)</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Previous stroke by MRI, % (n)</td>
<td>50.7% (70)</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Significant ECCA stenosis</td>
<td>13.8% (19)</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.0±0.3</td>
<td>1.1±0.2</td>
<td>1.1±0.2</td>
<td>0.062</td>
</tr>
<tr>
<td>White blood cell count (&lt;×10⁹/mL)*</td>
<td>8.0±2.4</td>
<td>6.2±1.0‡</td>
<td>5.9±0.6‡</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NIHSS at 48 hours ≥12, % (n)</td>
<td>50.0% (69)</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Circulating level of EPCs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD31/CD34 (%)*</td>
<td>2.25±2.17†</td>
<td>1.34±0.93‡</td>
<td>1.56±0.78†</td>
<td>0.035</td>
</tr>
<tr>
<td>CD62E/CD34 (%)*</td>
<td>2.25±2.20†</td>
<td>1.25±0.99‡</td>
<td>1.55±0.76‡</td>
<td>0.028</td>
</tr>
<tr>
<td>KDR/CD34 (%)*</td>
<td>2.17±1.94†</td>
<td>1.35±0.95‡</td>
<td>1.38±0.90†</td>
<td>0.025</td>
</tr>
<tr>
<td>Stain therapy</td>
<td>45.7% (63)</td>
<td>50.0% (20)</td>
<td>...</td>
<td>0.627</td>
</tr>
<tr>
<td>ACEI therapy</td>
<td>34.1% (47)</td>
<td>32.5% (13)</td>
<td>...</td>
<td>0.854</td>
</tr>
<tr>
<td>Recurrent stroke % (n)</td>
<td>2.2% (3)</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>90-day mortality % (n)</td>
<td>8.0% (11)</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or percent (no.) of patients.

*Arsine transformation of EPC expression and log transformation of white blood cell count were used to improve the normality for statistical analysis.

†,‡Significant difference (at 0.05 level) by Tukey multiple comparison procedure.

ECCA indicates extracranial carotid artery; ACEI, angiotensin-converting enzyme inhibitor.
determine the EPC surface markers of CD31/CD34 (E1), CD62E/CD34 (E2), and KDR/CD34 (E3), mononuclear cells (4×10^5) were incubated for 30 minutes at 4°C in a dark room with monoclonal antibodies against kinase insert domain-conjugating receptor (Sigma), the fluorescein isothiocyanate-conjugated CD34, and the phycocerythrin-conjugated CD31, and CD62E (Becton Dickinson). The control ligand (IgG-phycocerythrin conjugate) was used to detect any nonspecific association and define a threshold for glycoprotein binding. For analysis of kinase insert domain-conjugating receptor, the mononuclear cells were further incubated with phycocerythrin-conjugated anti-mouse antibody made in goat. After staining, the mononuclear cells were fixed in 1% of paraformaldehyde. Quantitative 2-color flow cytometric analysis was performed using a fluorescence-activated cell sorter (FACS Calibur system; Beckman). Each analysis included 30,000 cells per sample. The assays for EPCs (Ei–3) in each sample were performed in duplicated with mean level reported.

Intraassay variability based on repeated measurement of the same blood sample was low with mean coefficient of variance of 5.3% in patients with stroke, 4.8% in risk control subjects, and 4.6% in normal subjects.

Medications
Aspirin was the first choice for patients with acute stroke unless they were allergic or intolerant to aspirin such as having a history of peptic ulcer or upper gastrointestinal tract bleeding during aspirin therapy. Clopidogrel was used in patients intolerant to aspirin therapy. Other commonly used drugs included statins, angiotensin-converting enzyme inhibitors, calcium channel blocker agents, and β-blocker agents.

Statistical Analysis
Categorical data were analyzed by χ^2 test. Comparisons of means were performed using Student t test. Continuous variables among 3 groups were compared using one-way analysis of variance followed by Tukey multiple comparison procedure. When continuous data were compared, arsine transformation of EPC and log transformation for white blood cell count were used to improve normality. Multivariate logistic regression analysis was used for identifying the independent predictors of EPC level and prognostic outcomes. Statistical analysis was performed using SAS statistical software for Windows version 8.2 (SAS Institute, Cary, NC). A value of P < 0.05 was considered statistically significant.

Results
Baseline Characteristics of the 3 Groups
Table 1 displays baseline characteristics of the 3 groups. Body mass index was significantly higher in IS and at-risk control groups than in healthy control subjects. Additionally, white blood cell count was noticeably higher in patients with IS than in both control groups. Moreover, level of circulating EPCs (Ei–3) was substantially higher in patients with IS than in at-risk control subjects. However, level of circulating EPCs (Ei–3) did not differ between patients with IS and normal control subjects.

Comparison of Baseline Variables Between Patients with National Institutes of Health Stroke Scale ≥12 and Patients With National Institutes of Health Stroke Scale <12 and the Independent Predictors of Severe Neurological Impairment at 48 Hours After Ischemic Stroke
Univariate analysis demonstrated a significantly higher white blood cell count and significantly lower level of circulating EPCs (Ei–3) in patients with NIHSS ≥12 than in patients with NIHSS <12 at 48 hours after IS (Table 2).

Table 2. Comparison of Baseline Characteristics Between Patients with NIHSS ≥12 and Patients With NIHSS <12 at 48 Hours After Ischemic Stroke

<table>
<thead>
<tr>
<th>Variables</th>
<th>NIHSS ≥12 (n=69)</th>
<th>NIHSS &lt;12 (n=69)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>65.8±11.0</td>
<td>66.8±9.9</td>
<td>0.597</td>
</tr>
<tr>
<td>Male, % (n)</td>
<td>68.1% (47)</td>
<td>63.8% (44)</td>
<td>0.590</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>69.6% (48)</td>
<td>73.9% (51)</td>
<td>0.571</td>
</tr>
<tr>
<td>Diabetes mellitus, % (n)</td>
<td>42.0% (29)</td>
<td>42.0% (29)</td>
<td>1.0</td>
</tr>
<tr>
<td>Current smoking, % (n)</td>
<td>23.2% (16)</td>
<td>29.0% (20)</td>
<td>0.438</td>
</tr>
<tr>
<td>Hypercholesterolemia, % (n)</td>
<td>47.8% (33)</td>
<td>46.4% (32)</td>
<td>0.865</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.7±2.7</td>
<td>24.9±2.9</td>
<td>0.675</td>
</tr>
<tr>
<td>Previous stroke by history, % (n)</td>
<td>37.7% (26)</td>
<td>36.2% (25)</td>
<td>0.86</td>
</tr>
<tr>
<td>Previous stroke by MRI, % (n)</td>
<td>47.8% (33)</td>
<td>53.6% (37)</td>
<td>0.496</td>
</tr>
<tr>
<td>Significant ECCA stenosis</td>
<td>17.4% (12)</td>
<td>10.1% (7)</td>
<td>0.217</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.97±0.26</td>
<td>1.01±0.26</td>
<td>0.327</td>
</tr>
<tr>
<td>White blood cell count (×10^3/mL)</td>
<td>8.7±2.7</td>
<td>7.3±1.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Stain therapy</td>
<td>43.5% (30)</td>
<td>47.8% (33)</td>
<td>0.608</td>
</tr>
<tr>
<td>ACEI therapy</td>
<td>34.8% (24)</td>
<td>33.3% (23)</td>
<td>0.857</td>
</tr>
</tbody>
</table>

Circulating level of EPCs
| CD31/CD34 (%) | 1.54±1.26 | 2.95±2.62 | 0.0002 |
| CD62E/CD34 (%) | 1.55±1.52 | 2.94±2.55 | 0.0003 |
| KDR/CD34 (%) | 1.53±1.29 | 2.81±2.25 | 0.0002 |

Data are expressed as mean±SD or percent (no.) of patients. ECCA indicates extracranial carotid artery; ACEI, angiotensin-converting enzyme inhibitor.

Predictors of Improved National Institutes of Stroke Scale ≥4 Scores on Day 21 After Ischemic Stroke
Univariate logistic regression analysis revealed that no history of stroke and level of circulating EPCs (Ei–3) were significantly predictive of improvement of NIHSS ≥4 on day 21 after ischemic stroke (Table 4).

Multiple logistic regression analysis revealed that only high circulating level of EPCs (Ei–3) was a significant independent predictor of improvement of NIHSS ≥4 on day 21 after IS (odds ratio=0.76; 95% CI: 0.66 to 0.89; P=0.0004).

Impact of Level of Circulating Endothelial Progenitor Cells on 90-Day Clinical Outcomes
Three patients (2 with NIHSS of ≥12 on day 90 after IS) experienced recurrent IS 2 months later after first IS attack. Three patients died within 3 weeks after admission. Another
8 patients died more than 3 weeks but less than 3 months after IS. By day 90, the incidence of NIHSS ≥12 was 19.7% (25 of 127). Therefore, the 90-day combined major adverse clinical outcomes (defined as NIHSS of ≥12 on day 90 after IS, recurrent IS, or 90-day death) was 27.0% (37 of 138).

Univariate logistic regression analysis of baseline variables in Table 2 demonstrated that high level of circulating EPCs (E1) was significantly associated with absence of 90-day combined major adverse clinical outcomes (Table 5). Multiple logistic regression analysis of variables in Table 5 revealed that only level of circulating EPCs (E1–3) was significantly associated with absence of 90-day combined major adverse clinical outcomes.

**Discussion**

The present study of the level of circulating EPCs in patients after acute IS produced several clinically striking implications. First, level of circulating EPCs was significantly higher in patients with acute phase IS than in at-risk control subjects. Second, low level of circulating EPCs at 48 hours after IS was strongly and independently predictive of severe neurological impairment. Third, increased level of circulating EPCs at the acute phase of IS was independently predictive of improvement of NIHSS at the convalescence phase after IS. Finally, increased circulating level of EPCs at the acute phase of IS was independently predictive of freedom from 90-day combined major adverse clinical outcomes.

**Migratory Circulation of Endothelial Progenitor Cells in Response to Acute Ischemic Stroke**

Recent studies have documented rapidly increasing level of circulating EPCs in acute coronary syndrome and traumatic vascular injury compared with healthy subjects. The experimental results of this study also revealed that level of circulating EPCs increased rapidly in the acute phase of IS. Thus, the findings of this study are consistent with recent studies, and therefore, the findings of our and the recent studies indicate that mobilization of EPCs from bone marrow to circulation is a rapid response to tissue ischemia or injury. In contrast to our results and the findings from recent observational studies, Ghani et al recently demonstrated that the number of circulating EPCs was significantly lower in patients with cerebrovascular disease than in control subjects and was not significantly lower in patients with acute stroke compared with patients with stable vascular disease. We remain uncertain why our and recent findings are inconsistent with Ghani et al’s results. Interestingly, serial changes of circulating level of EPCs were demonstrated in patients after acute IS. Taking this finding and an acute response of EPC mobilization from bone marrow to tissue ischemia or injury into consideration, the difference in the time interval for blood sampling between the present and the recent studies and the Ghani et al study could, at least in part, explain this discrepancy.

Interestingly, the number and migratory activity of circulating EPCs has been reported to inversely correlate with risk factors for coronary artery disease and Framingham risk factor score. Additionally, circulating EPC number is reportedly to be somewhat lower in subjects with coronary artery disease.
Link Between Level of Circulating Endothelial Progenitor Cells and White Blood Cell Count and Clinical Outcomes After Ischemic Stroke

Increased white blood cell count has been associated with poor clinical outcomes in clinical studies of IS and acute coronary syndrome.\(^21,22\) The present study also found that increased white blood cell count was strongly and independently associated with severe neurological impairment at 48 hours after acute IS. Therefore, our finding further confirms the previous observational studies.\(^21,22\)

The impact of level of circulating EPCs on clinical outcomes after IS is currently uncertain. One important finding in the present study was that increased level of circulating EPCs was independently predictive of NIHSS <12 at the acute phase of IS. This finding suggests that raising numbers of circulating EPCs is an individualized and inherent response to brain tissue ischemia and infarction and is consistent with the angiogenesis, vasculogenesis, and the possibility of collateral formation in ischemic areas after acute IS. Recent studies revealed that bone marrow-derived circulating EPCs play an important role in repairing endothelial injury and participate directly in vasculogenesis and angiogenesis in systemic vascular beds.\(^23,24\) Additionally, contribution of EPCs in maintenance and repair of the cerebral vasculature has been demonstrated in settings of ischemic stress.\(^17\) Furthermore, myocardial homing of bone marrow-derived stem cells has also been identified after myocardial damage.\(^25\) Accordingly, the clinical observations and laboratory findings of this study are further supported by these recent studies.\(^23-25\)

Another important finding of this study was that increased levels of circulating EPCs at the acute phase of IS strongly correlates with improved NIHSS ≥4 score at the convalescent phase after IS. The most important finding of this study was that an increased level of circulating EPCs at the acute phase of IS is the only independent predictor of favorable 90-day clinical outcomes after IS. The findings of this study therefore suggest that the beneficial effect of increased EPCs in circulation, which is known to be essential in angiogenesis and vasculogenesis,\(^23,24\) is continuously translated from the acute to the chronic phase for functional recovery after acute IS. A recent study demonstrated that intravenous injection of granulocyte colony-stimulating factor exerting angiogenesis and mobilization of bone marrow-derived stem cells to the peripheral blood\(^26\) improves neurological outcomes after IS.\(^26,27\) The analytical results of these recent studies\(^26,27\) therefore support this observational study.

Notably, patients with recurrent IS in this study had a significantly lower level of circulating EPCs than patients with initial IS. This finding raises the suspicion that patients with low EPC numbers in circulation are unable to exert angiogenesis, vasculogenesis, repair of endothelial injury, and formation of collaterals after an IS attack. Arenillas et al\(^28\) recently demonstrated an association between an increased ratio of antiangiogenic endostatin to proangiogenic vascular endothelial growth factor in patients with significant intracranial stenoses and increased risk of future IS. Accordingly, the present findings further support the findings of the Arenillas et al study.\(^28\)

Study Limitations

It is practically impossible to routinely perform intracranial angiographic examination for patients with acute IS. Therefore, the impact of level of circulating EPCs on angiogenesis and collateral formation discussed in this study is speculative.

In conclusion, acute IS enhances EPC release to circulation. Increased level of circulating EPCs is strongly associated with a favorable clinical outcomes after IS. Therefore, the results of this study can be extended to more clinical implications, but further prospective studies are needed to evaluate whether level of circulating EPCs can serve as a valuable biological marker and permit the stratification of patients with IS into high- and low-risk groups with respect to future outcomes.

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Disclosures

None.

References


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