Relation Between White Blood Cell Counts and Myocardial Reperfusion in Patients With Recanalized Anterior Acute Myocardial Infarction

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Background  The clinical significance of the white blood cell (WBC) count on admission in relation to the duration of ischemia in acute myocardial infarction (AMI) remains unclear.

Methods and Results  The relationship of the WBC count on admission to myocardial reperfusion was examined in 135 patients with recanalization of an anterior AMI within 6 h of symptom onset. Patients were classified according to the WBC count on admission: Group L (n=75), WBC count <12,000 cells/mm³ and group H (n=60), WBC count ≥12,000 cells/mm³. Peak creatine kinase (CK) was higher and impaired myocardial reperfusion, defined as a myocardial blush grade of 0/1, was more frequent in group H than in group L. Among the patients in group H, those with early (≤3 h) recanalization had a lower QRS score before recanalization than those with late (>3 h) recanalization; however, peak CK and the incidence of impaired myocardial reperfusion were similar in these subgroups of patients. Multivariate analysis showed that WBC count ≥12,000 cells/mm³ on admission was an independent predictor of impaired myocardial reperfusion in patients with early recanalization (odds ratio 7.9, p=0.04), but not in those with late recanalization.

Conclusions  A higher WBC count may be associated with progression of myocardial damage after recanalization in patients with early recanalization of an anterior AMI.  (Circ J 2004; 68: 526–531)

Key Words:  Blood cells; Myocardial infarction; Reperfusion

The white blood cell (WBC) count on admission is a strong and independent predictor of increased morbidity and mortality in patients with acute myocardial infarction (AMI) although the mechanism underlying these observations is unclear. Recent studies have reported that an elevated WBC count on admission is associated with a larger infarct size but whether it is the cause or the result of the large infarct remains to be determined. The development of ischemic myocardial damage may time-dependently elevate the WBC count in patients with AMI suggesting that the WBC count during the acute phase of AMI may be affected by the duration of the ischemia. Previous studies have assessed the relation between the WBC count and infarct size, without examining ischemic time, so the present study sought to clarify the relation of the WBC count on admission to infarct size and myocardial reperfusion according to ischemic time in patients with a recanalized anterior AMI.

Methods

Study Group

The study group comprised 135 consecutive patients (mean age 59±11 years; 111 men, 24 women) with an AMI who fulfilled the following criteria: (1) no history of myocardial infarction; (2) complete occlusion (TIMI grade 0 flow) of the left anterior descending (LAD) coronary artery on admission with achievement of TIMI grade 3 flow as confirmed by coronary angiography within 6 h of symptom onset; (3) normal electrocardiograms (ECGs) obtained before and after recanalization; (4) adequate assessment of myocardial blush grade after recanalization; (5) a patent LAD coronary artery as confirmed by predischarge coronary angiography, performed a mean of 14 days after AMI; and (6) no concomitant noncardiac diseases, such as inflammatory disorders, malignancy, or infection. The diagnosis of anterior AMI was based on typical chest pain lasting more than 30 min, ST-segment elevation of at least 2 mm in at least 2 contiguous precordial leads, and a subsequent increase in the serum creatine kinase (CK) concentration to more than twice the upper limit of normal.

Coronary Angiography

Coronary angiography was performed immediately after admission. The grade of collateral filling in the LAD coronary artery was evaluated as described by Rentrop et al.28 A good collateral channel was defined as grade 2 or 3, and a poor collateral channel as grade 0 or 1. The allocation of recanalization therapy was left to the attending doctor’s discretion.28 Recanalization was defined as the establishment of TIMI grade 3 flow. In the right coronary artery and the left circumflex coronary artery, stenosis was considered clinically significant if the lumen diameter was narrowed by 75% or more in any projection. Myocardial blush was
graded as follows on angiograms obtained immediately after recanalization by 2 observers who were unaware of all data apart from the coronary angiograms: 0, no myocardial blush or contrast density; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density, but less than that obtained during angiography of a contralateral or ipsilateral noninfarct-related coronary artery; and 3, normal myocardial blush or contrast density, comparable to that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery. When myocardial blush persisted, this finding was graded as 0.

### Electrocardiographic Analysis

Standard 12-lead ECGs were recorded at least every 10 min during recanalization therapy at a paper speed of 25 mm/s and an amplification of 10 mm/mV. The isoelectric line was defined as the level of the preceding TP segment. ST-segment elevation was measured to the nearest 0.5 mm 10 min during recanalization by 2 independent observers unaware of all clinical and angiographic findings. Additional ST-segment elevation of at least 5 mm in leads V1–6 immediately after recanalization was defined as ST-segment re-elevation.10,11 In addition, the ECGs were scored according to the 32-point QRS score before and 1 h after recanalization (QRSpre, QRSPost).12 The QRS score was additionally determined a mean of 14 days after AMI (QRSD14). This QRS score has been validated in patients with AMI and determined a mean of 14 days after AMI (QRSD14). This

### Blood Samples

Routine blood samples for measuring the peripheral WBC count were taken on admission and samples for measurement of serum CK were taken on admission, every 3 h during the first 24 h, every 6 h for the next 2 days, and then daily until discharge.

### Analysis of Left Ventricular Function

Left ventricular function was evaluated on right anterior oblique views of left ventriculograms obtained a mean of 14 days after AMI. Left ventricular end-diastolic volume index, end-systolic volume index (LVESVI), and left ventricular ejection fraction (LVEF) were determined by the area-length method as described by Sandler and Dodge.15 Regional wall motion in the territory of the LAD coronary artery was assessed with the centerline method and expressed as standard deviation (SD)/chord.

### Statistical Analysis

Data are expressed as mean values ± standard deviation for continuous variables and as percentages for categorical variables. Continuous variables were compared with non-parametric tests (Mann-Whitney U test between groups). Chi-square analysis was used to compare categorical variables. A probability value <0.05 was considered to indicate a statistically significant difference. Multiple logistic regression analysis was used to examine determinants of impaired myocardial reperfusion. Impaired myocardial reperfusion, defined as a myocardial blush grade of 0 or 1, was the dependent variable. The independent variables were age, sex, previous angina within 24 h before AMI, systolic blood pressure and heart rate on admission, WBC count ≥12,000 cells/mm³ on admission, multivessel disease, culprit lesion, good collateral circulation, method of reperfusion therapy, and QRS score before recanalization. Odds ratios and 95% confidence intervals (CI) were calculated. Analyses were done using SPSS PC software (Chicago, IL, USA).
Results

Baseline Characteristics

Patients were classified according to the WBC count on admission: group L, WBC count <12,000 cells/mm³ (a mean value) and group H, WBC count ≥12,000 cells/mm³. The baseline characteristics are presented in Table 1. Group H patients were younger and had a lower incidence of previous angina within 24 h before AMI and a higher incidence of smoking. There was a trend toward a higher incidence of ST-segment re-elevation in group H, but this did not reach statistical significance. Among the patients with ST-segment re-elevation, the increase in ST-segment elevation immediately after recanalization was significantly greater and the proportion of patients who had an abrupt increase in chest pain requiring morphine during recanalization was significantly higher in group H than in group L. The other baseline clinical and angiographic characteristics were similar in the 2 groups. Patients in group H were subdivided into 2 groups according to the time from symptom onset to recanalization: early (≤3 h) and late (>3 h) recanalization. Patients with early recanalization had higher frequencies of ST segment re-elevation and an abrupt increase in chest pain during recanalization than those with late recanalization. There was a trend toward a greater increase in ST-segment elevation immediately after recanalization in patients with early recanalization, but this did not reach statistically significant difference (Table 2).

Severity of Myocardial Damage Before and After Recanalization

QRSpre, QRSpost, and QRS14 were significantly greater in group H than in group L (Table 1). Fig 1 shows the changes in the QRS scores of the patients in group H according to the time from symptom onset to recanalization. The QRSpre was significantly lower in patients with early recanalization than in those with late recanalization. After recanalization, there was no difference in the QRSpost between patients with early and late recanalization. Therefore, the increment in QRS score (QRSpost – QRSpre) was significantly greater in patients with early recanalization than in those with late recanalization. During the next 14 days, there were no significant changes in QRS score (QRS14 – QRSpost) between patients with early or late recanalization.

Myocardial Reperfusion After Recanalization

Impaired myocardial reperfusion as indicated by a myocardial blush grade of 0 or 1 was significantly more frequent in group H than in group L (Table 3). When pa-
Patients in group H were subdivided into 2 groups according to the time from symptom onset to recanalization, the incidence of impaired myocardial reperfusion was similar in patients with early or late recanalization (Table 4).

### Infarct Size and Left Ventricular Function at Discharge

Patients in group H had a significantly higher peak CK concentration, a lower LVEF, lower regional wall motion, a lower LVEF, lower regional wall motion, and a higher LVESVI than those in group L (Table 3). When patients in group H were subdivided into 2 groups according to the time from symptom onset to recanalization, peak CK and left ventricular function were similar in patients with early or late recanalization (Table 4).

### Multivariate Analysis

Multivariate analysis showed that in patients with early recanalization, both a WBC count ≥12,000 cells/mm³ on admission and the absence of previous angina were independently associated with impaired myocardial reperfusion as indicated by a myocardial blush grade of 0 or 1. In patients with late recanalization, the QRS score before recanalization was independently associated with impaired myocardial reperfusion (Table 5).

### Discussion

The present study demonstrated that a higher WBC count on admission, defined as WBC count ≥12,000 cells/mm³, was associated with a larger infarct size and impaired myocardial reperfusion as indicated by myocardial blush grade of 0 or 1, in agreement with previous reports. Among patients who had a higher WBC count on admission, infarct size and myocardial reperfusion were similar in patients with early recanalization (≤3 h) and those with late recanalization (>3 h), but the QRS score suggested that myocardial damage might have progressed rapidly after recanalization in the former group. Multivariate analysis showed that a higher WBC count on admission was independently associated with impaired myocardial reperfusion in patients with early recanalization. These findings suggest that a higher WBC count might be associated with progression of myocardial damage after recanalization in patients with AMI who have early recanalization.

Several factors must be considered when assessing the relation between the WBC count and infarct size. WBCs are a component of the acute phase response, and experimental studies have shown that neutrophil infiltration of the

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### Table 3 Myocardial Reperfusion, Infarct Size and Predischarge Left Ventricular Function in All Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group L (n=75)</th>
<th>Group H (n=60)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial blush grade 0/1</td>
<td>31 (52%)</td>
<td>31 (52%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak CK (mU/ml)</td>
<td>3,722±2,214</td>
<td>5,453±2,802</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>46±12</td>
<td>46±12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SD/chord</td>
<td>2.2±1.0</td>
<td>2.4±0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>38±18</td>
<td>46±17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>77±20</td>
<td>83±22</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD or number (%) of patients.

### Table 4 Myocardial Reperfusion, Infarct Size and Predischarge Left Ventricular Function in Patients in Group H

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early (≤3 h) recanalization (n=24)</th>
<th>Late (&gt;3 h) recanalization (n=36)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial blush grade 0/1</td>
<td>18 (50%)</td>
<td>13 (54%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Peak CK (mU/ml)</td>
<td>5,574±2,692</td>
<td>5,317±3,009</td>
<td>0.77</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>46±12</td>
<td>45±11</td>
<td>0.84</td>
</tr>
<tr>
<td>SD/chord</td>
<td>2.4±0.9</td>
<td>2.4±0.9</td>
<td>0.85</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>48±17</td>
<td>48±17</td>
<td>0.72</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>85±21</td>
<td>83±24</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD or number (%) of patients.

### Table 5 Multivariate Analysis of Factors Associated With Impaired Myocardial Perfusion After Recanalization in All Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early (≤3 h) recanalization (n=62)</th>
<th>Late (&gt;3 h) recanalization (n=73)</th>
<th>Odds ratio (95% CI) p value</th>
<th>Odds ratio (95% CI) p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.93 (0.84–1.04)</td>
<td>1.01 (0.91–1.11)</td>
<td>0.979</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.33 (0.02–7.17)</td>
<td>1.25 (0.09–16.9)</td>
<td>0.868</td>
<td></td>
</tr>
<tr>
<td>Absence of previous angina</td>
<td>6.29 (1.24–11.7)</td>
<td>4.06 (0.02–136)</td>
<td>0.154</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure on admission</td>
<td>0.98 (0.94–1.02)</td>
<td>1.02 (0.98–1.07)</td>
<td>0.269</td>
<td></td>
</tr>
<tr>
<td>Heart rate on admission</td>
<td>0.99 (0.97–1.02)</td>
<td>1.02 (0.95–1.09)</td>
<td>0.629</td>
<td></td>
</tr>
<tr>
<td>Elevated WBC count on admission*</td>
<td>7.85 (1.15–33.9)</td>
<td>1.84 (0.12–5.87)</td>
<td>0.459</td>
<td></td>
</tr>
<tr>
<td>QRS score before recanalization</td>
<td>1.56 (0.87–2.82)</td>
<td>3.00 (1.57–5.71)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>1.49 (0.06–4.31)</td>
<td>3.12 (0.43–22.5)</td>
<td>0.258</td>
<td></td>
</tr>
<tr>
<td>Culprit lesion (Seg. 6)</td>
<td>1.26 (0.21–7.45)</td>
<td>1.23 (0.16–9.17)</td>
<td>0.843</td>
<td></td>
</tr>
<tr>
<td>Good collateral circulation†</td>
<td>0.19 (0.02–1.52)</td>
<td>0.18 (0.03–1.31)</td>
<td>0.090</td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>2.07 (0.34–12.6)</td>
<td>1.61 (0.26–9.95)</td>
<td>0.606</td>
<td></td>
</tr>
</tbody>
</table>

*WBC count ≥12,000 cells/mm³; †Grade 2 or 3 collateral flow to the left anterior descending coronary artery.
ischemic myocardium is apparent 3–6h after coronary occlusion, with an acute increase in the number of neutrophils entrapped in the ischemic myocardium after reperfusion.\textsuperscript{17,18} Other studies have suggested that the development of myocardial ischemic damage may time-dependently elevate the WBC count in patients with AMI.\textsuperscript{7} Various factors, including the time elapsed from coronary occlusion, the presence or absence of coronary reperfusion, and the time of evaluating the WBC count, may affect the WBC count during the acute phase of AMI. In most previous clinical studies assessing the relation between the WBC count and infarct size, the patient population has been heterogeneous with respect to these factors. In our study, we measured WBC counts before recanalization, within 6h after the onset of AMI. To minimize the effects of disparate clinical characteristics, all patients had to have total occlusion of the proximal or mid LAD coronary artery and successful recanalization, with no evidence of reocclusion on coronary angiography at discharge.

Our electrocardiographic findings indicated that patients with a higher WBC count on admission who underwent early recanalization had less myocardial damage before recanalization than those who underwent late recanalization, but had severe myocardial damage after recanalization. This assumption is supported by a lower QRS score, more frequent ST-segment re-elevation with a greater increase in ST-segment elevation, a marker of microcirculatory reperfusion injury,\textsuperscript{19} and severer chest pain in the patients with early recanalization. Consequently, there were no differences between the 2 groups in myocardial damage after recanalization. Multivariate analysis showed that a higher WBC count on admission was an independent predictor of impaired myocardial reperfusion as indicated by a myocardial blush grade of 0 or 1 in patients with early recanalization. Experimental studies have shown that neutrophils plug myocardial capillaries and lead to a capillary no-reflow phenomenon after reperfusion.\textsuperscript{20} Those findings support the notion that an elevated WBC count may directly cause further myocardial and microvascular damage in patients with early recanalization, consistent with the results of several experiments in animals.\textsuperscript{18,20–22} In contrast, extensive myocardial damage might have been present before recanalization in patients with a higher WBC count who had late recanalization, as suggested by the higher QRS score. The longer elapsed time from coronary occlusion as well as more severe myocardial damage could have elevated the WBC count. In patients who had late recanalization, multivariate analysis showed that the QRS score before recanalization, not a higher WBC count, was an independent predictor of impaired myocardial reperfusion. These findings are in accord with the results of Iwakura et al\textsuperscript{23} who found that more severe myocardial damage before recanalization, as indicated by a greater number of Q waves on admission ECGs, is closely related to the no-reflow phenomenon in patients with successful coronary recanalization after angioplasty.

Although several experimental studies have shown that inhibition of leukocyte adhesion by treatment with an anti-CD18 antibody can reduce myocardial infarct size,\textsuperscript{24,25} a recent report in humans did not show the effect of anti-CD18 antibody treatment on infarct size.\textsuperscript{26} The discrepancy between the results of the experimental and human studies may be attributed to the optimal timing or dosage of administration. Therefore, our results suggest that therapeutic strategies aimed at reducing the deleterious inflammatory effects of WBC may be most effective in patients who have higher WBC counts during the hyperacute phase of AMI. Recently, the AMISTAD-II trial\textsuperscript{27} demonstrated that the beneficial effects of adenosine, which inhibits neutrophil activity and accumulation,\textsuperscript{28} were amplified when reperfusion treatment was given early (<2h) after infarction. This finding might support our results, but firm conclusions must await the outcome of future research exploring the relation between the inflammatory effects of WBC and infarct size.

Study Limitations

First, this was a small retrospective study of patients who met strict entry criteria. However, we believe that these criteria enabled us to demonstrate more clearly the relation of the WBC count to myocardial and microvascular damage during AMI. Second, we did not collect data on specific types of WBCs, which may have provided important additional information.

Conclusions

Our findings suggest that a higher WBC count might be associated with progression of myocardial damage after recanalization in patients with AMI who have early recanalization.

References


