The prognostic value of interleukin (IL)-18 in patients with ST-segment elevation acute myocardial infarction (STEMI) is currently unclear. Thus, the purpose of this study was to test whether the circulating IL-18 level can predict prognosis in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

**Methods and Results** A prospective cohort study was conducted with 267 consecutive patients with STEMI of onset <12 h who were undergoing primary PCI. Blood samples for plasma IL-18 level were collected in the catheterization laboratory following vascular puncture. The plasma IL-18 level was also evaluated in 25 healthy and 30 at-risk control subjects. The plasma level of IL-18 was significantly higher in acute myocardial infarction (AMI) patients than in both groups of control subjects (all p<0.0001). Patients with high plasma IL-18 level (≥560 pg/ml) had significantly higher peak creatine kinase-MB levels, higher incidence of cardiogenic shock upon presentation, significantly lower left ventricular ejection fraction (LVEF), lower successful reperfusion and significantly higher incidence of 30-day composite major adverse clinical events (MACE) (advanced congestive heart failure ≥ class 3 or 30-day mortality) than those patients with low plasma IL-18 level (<560 pg/ml) (all p<0.0001). Multiple stepwise logistic regression analysis demonstrated that high plasma IL-18 level (≥560 pg/ml) along with low LVEF (<50%) and cardiogenic shock were the most independent predictors of 30-day MACE (p<0.0001).

**Conclusions** In patients with STEMI, plasma IL-18 level is a major independent inflammatory predictor of 30-day MACE. Evaluation of circulating IL-18 might improve the prediction of unfavorable clinical outcomes following AMI. (Circ J 2007; 71: 703–708)

**Key Words:** Acute myocardial infarction; Interleukin-18; Major adverse clinical outcomes

Acute myocardial infarction; Interleukin-18; Major adverse clinical outcomes plays an essential role in myocardial necrosis and microvascular reperfusion injury in patients with ACS. Therefore, the rationale is that inflammatory mechanisms have an important role in the occurrence of AMI and that inflammatory cytokines could be useful as predictors of clinical outcomes following AMI. Although investigators are likely to address whether some inflammatory markers are superior to others or add some complementary findings by simultaneous determination, comparative data for single inflammatory markers are sparse.

Interleukin (IL)-18 is a member of the IL-1 family of cytokines and is processed, like IL-1β, by caspase 1. Originally, IL-18 was identified as an interferon-β-inducing factor stimulating interferon-β-induction in T lymphocytes and natural killer cells, which have been ascribed a key role in atherosclerotic plaque rupture. There is increasing data to demonstrate that IL-18 is a pleiotropic proinflammatory cytokine acting in both acquired and innate immunity, and plays a crucial role in the inflammatory cascade. Recent evidence from experimental studies has demonstrated that IL-18 is intimately related to atherosclerotic plaque propagation and instability. Additionally, IL-18 has been found to be independently predictive of future coronary events in both coronary disease and healthy subjects. Although 1 previous small study dem-
onstrated that IL-18 was markedly increased and correlated with myocardial injury in patients following AMI\(^5\) the prognostic value of IL-18 in the clinical setting of AMI is currently unknown. Thus, the purpose of this study was to evaluate the circulating level of IL-18 and its relationship with prognostic outcomes in patients with AMI undergoing primary percutaneous coronary intervention (PCI).

**Methods**

**Patient Population and Inclusion Criteria**

All patients with AMI were considered eligible for primary PCI. For the purpose of this study, blood samples for plasma IL-18 levels were drawn into EDTA tubes in the cardiac catheterization room following vascular puncture. To circumvent other potential influences on the circulating level of IL-18, we excluded patients with a history of recent surgery or trauma during the preceding 2 months, renal insufficiency (creatinine >1.5 mg/dl), malignancy, febrile disorders, acute or chronic inflammatory disease at study enrollment, autoimmune diseases with or without immunosuppressive therapy, or a prior myocardial infarction (MI) <3 months. Thus, between November 2002 and May 2004, 267 consecutive patients of any age, who presented with AMI <12h duration and underwent primary PCI were prospectively investigated and recruited.

Thirty subjects matched for age, gender, hypertension, diabetes mellitus, current smoking and hypercholesterolemia were assigned as the at-risk control group and an additional 25 age- and gender-matched healthy volunteers were assigned as the healthy control group. Informed consent was obtained from each study subject. The Institutional Review Committee on Human Research approved the study protocol.

**Procedure and Protocol**

A transradial artery approach using a 6Fr arterial sheath was routinely used for treatment of AMI unless the Allen’s test was positive for both hands. A 6Fr Kimny Miniradial guiding catheter (Boston Scientific, Scimed, Inc, Maple Grove, MN, USA) was used for diagnosis and primary PCI. Immediately after coronary angioplasty, left ventriculograms were recorded in the 30° right anterior oblique and 60° left anterior oblique views.

At the beginning of this study the tirofiban loading dose (20 \(\mu g/kg\)) was administered to patients on presentation in the emergency room, followed by a maintenance infusion of 0.15 \(\mu g·kg^{-1}·min^{-1}\) for 18–24h. However, tirofiban therapy was subsequently withheld because it was found not to provide any additional benefit to AMI patients who underwent primary PCI\(^6\). Therefore; only 49 (18.4%) patients received tirofiban therapy. From May 2002, the PercuSurge GuardWire\™ device (Medtronic AVE) was used. Enrollment and exclusion criteria and the procedure of using PercuSurge have been previously described in detail\(^7\).

Clopidogrel (300 mg loading dose before stenting then 75 mg/day) was given to patients who underwent primary stenting. Aspirin (100 mg orally daily) was given indefinitely to each patient. Other drugs commonly prescribed were angiotensin-converting enzyme inhibitors (ACEI), \(\beta\)-blockers, isonitrate and diuretics.

**Blood Sampling and Laboratory Investigations**

Blood samples were obtained from the healthy volunteers during healthy clinic examination, and from the at-risk control subjects in the outpatient department. Venous blood was withdrawn from the antecubital vein into EDTA tubes. After centrifugation, aliquots of the samples were stored at −80°C before assay for IL-18. White blood cell (WBC) counts and biochemical measurements were done using standard laboratory methods.

Plasma IL-18 levels were measured by duplicate determination with a commercially available ELISA method (B & D; analytical range 5–5,000 pg/ml). The intra-individual variability was assessed in the patients and both control groups. The mean intra-assay coefficients of variance were all less than 4.0%. The levels of high-sensitivity C-reactive protein (hs-CRP) were measured by immunonephelometry using the BN™ system (Dade Behring Inc, Newark, DE, USA; lower detection limit <0.15 mg/L). The intra-individual variability was assessed in the 3 groups and the mean intra-assay coefficients of variance were 2.86%, 2.77%, and 2.81%, respectively.

**Definitions and Data Collection**

AMI was defined as the presence of typical chest pain for more than 30 min with ST-segment elevation >1 mm in 2 or
more consecutive precordial or inferior leads. Unsuccessful reperfusion was defined as failure to achieve normal blood flow after PCI (≤Thrombolysis in Myocardial Infarction [TIMI]-2 flow) of the infarct-related artery. Reperfusion time was defined as the time from chest pain onset to the first balloon inflation. Detailed in-hospital and follow-up data, including age, sex, coronary risk factors, serial MB fraction of creatine kinase (CK-MB) levels, WBC counts, platelet counts, creatinine level, body temperature, Killip score on admission, severity of congestive heart failure (CHF), angiographic findings and number of diseased vessels, were collected prospectively and entered into a computerized database.

Endpoints and Statistical Analysis

The study endpoint was the 30-day composite occurrence of major adverse clinical events (MACE), including advanced CHF (defined as New York Heart Association functional class ≥3) or 30-day death. The baseline variables were used for univariate analysis. All of the univariate significant factors were further used for multiple stepwise logistic regression analysis.

Data are expressed as mean±SD. Categorical variables were compared using chi-square or Fischer’s exact test. Continuous variables between 2 groups were analyzed by Wilcoxon’s rank sum test. Continuous variables among 3 groups were compared using the Kruskal-Wallis test, followed by posthoc multiple comparison procedure with the Wilcoxon’s rank sum test and Bonferroni’s correction. Discriminate analysis was used to find the cut-off value of IL-18 that was the most significant with good sensitivity and specificity for predicting 30-day MACE. Statistical analysis was performed using SAS statistical software for Windows version 8.2 (SAS Institute, Cary, NC, USA). A value of p<0.05 was considered statistically significant.

Results

Baseline Characteristics of AMI Patients, At-Risk Control Subjects and Healthy Control Subjects (Table 1)

There was neither significant difference among the 3 groups for age and gender nor between AMI patients and the at-risk control subjects for coronary artery disease risk factors. However, the hs-CRP level, WBC counts and IL-18 level were significantly higher in AMI patients than in the at-risk control and healthy control subjects. Additionally, the hs-CRP level was significantly higher in the at-risk control subjects than in the healthy control subjects.

Baseline Characteristics, Laboratory Findings, Angiographic Results, and 30-Day Clinical Outcomes for AMI Patients (Table 2)

The plasma IL-18 level ≥560 pg/ml was the most powerful cut-off value identified using the discriminating test for predicting 30-day MACE, with a sensitivity of 84.7% and a specificity of 90.4%. Thus, patients with a plasma IL-18 level ≥560 pg/ml were classified into the high level group (Group 1) and those with a plasma level <560 pg/ml were assigned to the low level group (Group 2). Except for age and current smoking, these 2 groups were similar in gender, cardiovascular risk factors, previous MI, previous stroke, incidence of tirofiban therapy and mean reperfusion time.
However, the WBC counts, plasma levels of hs-CRP and IL-18, and peak level of CK-MB were substantially higher in Group 1 than in Group 2 patients. Furthermore, the incidence of cardiogenic shock and advanced CHF were remarkably higher in Group 1 than in Group 2 patients. There was no significant difference in the frequency of using the PercuSurge device or stenting between Group 1 and Group 2 patients. However, the incidence of anterior wall infarction and multivessel disease were significantly higher in Group 1 than in Group 2, whereas LVEF, pre-PCI TIMI flow ≥2 in the infarct-related artery and successful reperfusion were markedly lower in Group 1 patients than in Group 2 patients. Moreover, Group 1 patients had a noticeably higher 30-day mortality rate than Group 2 patients.

Correlation analysis demonstrated that there was a significant direct relationship between the IL-18 level and CK-MB peak level (r=0.469, p<0.0001).  

**Determinants of 30-Day Composite MACE**

Table 3 presents the results of univariate analysis for factors associated with composite 30-day MACE. The most significant factors were high IL-18 level (≥560 pg/ml), peak CK-MB level, cardiogenic shock, and LVEF ≤50%.

**Table 3  Univariate Stepwise Logistic Regression Analysis of Variables Relevant to 30-Day Major Adverse Clinical Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (≥70 vs &lt;70)</td>
<td>2.97</td>
<td>1.63–5.40</td>
<td>0.0004</td>
</tr>
<tr>
<td>Female vs male</td>
<td>1.84</td>
<td>0.95–3.55</td>
<td>0.068</td>
</tr>
<tr>
<td>With vs without hypertension</td>
<td>0.97</td>
<td>0.56–1.70</td>
<td>0.921</td>
</tr>
<tr>
<td>With vs without diabetes mellitus</td>
<td>2.03</td>
<td>1.14–3.61</td>
<td>0.016</td>
</tr>
<tr>
<td>With vs without current smoking</td>
<td>1.07</td>
<td>0.61–1.87</td>
<td>0.814</td>
</tr>
<tr>
<td>With vs without hypercholesterolemia</td>
<td>0.82</td>
<td>0.47–1.44</td>
<td>0.494</td>
</tr>
<tr>
<td>IL-18 (≥560 vs &lt;560)* (pg/ml)</td>
<td>27.61</td>
<td>13.35–57.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak level of CK-MB (UL)</td>
<td>1.00</td>
<td>0.99–1.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>hs-CRP level (mg/L)</td>
<td>0.99</td>
<td>0.98–1.01</td>
<td>0.229</td>
</tr>
<tr>
<td>WBC counts (×10³/ml)</td>
<td>0.89</td>
<td>0.83–0.97</td>
<td>0.004</td>
</tr>
<tr>
<td>With vs without anterior wall infarction</td>
<td>2.54</td>
<td>1.41–4.57</td>
<td>0.002</td>
</tr>
<tr>
<td>With vs without cardiogenic shock</td>
<td>17.98</td>
<td>8.09–39.94</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>With vs without multi-vessel disease</td>
<td>2.61</td>
<td>1.46–4.69</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean reperfusion (&gt;240 vs ≤240 min)</td>
<td>1.08</td>
<td>0.61–1.91</td>
<td>0.785</td>
</tr>
<tr>
<td>Post-procedure TIMI-flow (3 vs ≤2)</td>
<td>0.28</td>
<td>0.12–0.65</td>
<td>0.003</td>
</tr>
<tr>
<td>LVEF (%) (&lt;50 vs ≥50)</td>
<td>12.59</td>
<td>6.57–24.14</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2.

*Percentage of IL-18 level ≥560 pg/ml found to be the most powerful cut-off value using the discriminating test for predicting 30-day composite major adverse clinical outcomes (defined as advanced congestive heart failure ≥ class 3 or 30-day death).

**Table 4  Multiple Stepwise Logistic Regression Analysis of Independent Predictors for 30-Day Major Adverse Clinical Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-18 ≥560 (pg/ml)</td>
<td>12.74</td>
<td>5.28–30.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF &lt;50%</td>
<td>6.60</td>
<td>2.67–16.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (≥70 years)</td>
<td>3.47</td>
<td>1.33–9.03</td>
<td>0.011</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>12.29</td>
<td>3.86–39.13</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1–3.

**Table 5  Multiple Stepwise Logistic Regression Analysis of Independent Predictors for 30-Day Mortality**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-18 ≥560 (pg/ml)</td>
<td>33.0</td>
<td>6.95–156.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>6.41</td>
<td>2.17–18.95</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1–3.

The present study, in which the circulating levels of inflammatory biomarkers and clinical relevant variables were examined in patients with STEMI undergoing primary PCI, produced several striking clinical implications. First, patients with high circulating IL-18 level had a
30-day mortality rate >33-fold higher than that of patients with a low circulating IL-18 level. Second, there was a strong independent association between increasing IL-18 level and 30-day mortality and MACE. Third, the results confirmed those of previous observation studies in which cardiogenic shock, low LVEF and older age were predictive of 30-day MACE in AMI patients. The present study, therefore, further strengthened the suggestion that the impact of these 3 clinically relevant factors on MACE was independent of the use of primary PCI.

Interleukin-18 acts directly as a proinflammatory cytokine by inducing IL-10, IL-12, and the expression of adhesion molecules. IL-18 is also able to stimulate the production of granulocyte-macrophage colony-stimulating factor, tumor necrotic factor-α, and inducible nitric oxide synthetase by mononuclear and mesenchymal cells. Surprisingly, in view of the potent inflammatory activities of IL-18, data addressing the prognostic value of the circulating level of IL-18 in STEMI patients undergoing primary PCI are not available. To the best of our knowledge, the present study is the largest and first cohort study to evaluate the impact of the circulating levels of IL-18 in such patients. One important finding of this study, consistent with that of a previous study, is that the plasma level of IL-18 is substantially higher in AMI patients than in either at-risk or normal control subjects. We remain uncertain about when, how fast and the mechanisms by which IL-18 is released into the circulation following AMI. However, compared with the baseline IL-18 level of the present at-risk control subjects, and based on previous observation studies, we suggest that the level of circulating IL-18 is rapidly and markedly increased immediately following AMI. A previous study found that the plasma IL-18 level elevated quickly after severe myocardial ischemia, which supports our suggestion. Additionally, previous studies have clearly shown that an acute elevation of inflammatory mediators occurs following ACS and another found that AMI induced cardiac release of cytokines and inflammatory responses. Moreover, an experimental study demonstrated that cytokine gene expression was induced rapidly following AMI. Accordingly, we suggest that the rapidly increased circulating level of IL-18 in the present patients was mainly a result of myocardial injury following AMI, which in turn mediated an acute inflammatory response.

Convincing data support that IL-18 directly participates in vascular inflammation; however, the contribution of IL-18 to myocardial damage in the clinical setting of AMI is currently unclear. Another important finding in this investigation was that patients with a higher circulating level of IL-18 had a significantly lower pre-interventional TIMI flow (grade ≥2) and less successful reperfusion than those patients with a lower circulating level of IL-18. Additionally, the circulating level of IL-18 strongly correlated with peak CK-MB levels, low LVEF and high incidences of advanced CHF, cardiogenic shock and anterior wall MI. Moreover, the hs-CRP level was significantly higher in patients with a high IL-18 level than in those with a low IL-18 level. Accordingly, we suggest that IL-18 directly participates in damaging the integrity of the microvasculature, microvascular reperfusion injury and myocardial damage through the inflammatory response. Recent studies have demonstrated that a robust inflammatory response is an integral component of the response to tissue injury and plays a particularly active role after AMI. Evidence also supports that rapidly and markedly increased circulating levels of neurohormones or inflammatory cytokines, which in turn elicit overreactive responses systemically, are harmful to AMI patients. Additionally, in the acute phase of AMI, circulating levels of CRP, an index of inflammation, are likely to predominantly reflect the inflammatory response to myocardial necrosis rather than by chronic vascular inflammation. Moreover, an association between increased circulating cytokines and microvascular reperfusion injury has been identified. Furthermore, cytokines originating from the myocardium or infiltrating inflammatory cells contribute to the raised CRP concentrations observed in patients with AMI. Accordingly, our suggestion, based on our findings, is further supported by the findings of these studies.

**Conclusion**

The present study demonstrated that the circulating level of IL-18 was substantially increased in patients with STEMI. We suggest its use as a marker of the acute inflammatory process and an index of myocardial necrosis. Additionally, a higher circulating IL-18 level (≥560 pg/ml) on admission is strongly associated with increased 30-day MACE and death. These findings highlight the use of the circulating IL-18 level for risk stratification of patients with AMI.

**References**


19. Gupta S, Pablo AM, Jiang X, Wang N, Tall AR, Schindler C. IFN- 


