Level and Value of Interleukin-18 in Patients With Acute Myocardial Infarction Undergoing Primary Coronary Angioplasty

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Background 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 $\geq$ 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

Atherosclerosis is intimately associated with an inflammatory process^{1,2} and there is now plenty of data to demonstrate that vulnerable plaque is characterized by accumulation of inflammatory cells, particularly macrophages and T lymphocytes^{2–4}. These inflammatory cells of unstable plaques produce high levels of the inflammatory cytokines that are responsible for the detrimental effects of plaque composition (ie, decreased number of smooth muscle cells and amount of collagen)^{1,3,5–7} which subsequently lead to plaque rupture and acute coronary syndrome (ACS)^{2–4,8}. Much of the evidences has also demonstrated that acute myocardial infarction (AMI) is associated with inflammation^{2,8–11} and that inflammation

plays an essential role in myocardial necrosis¹² and microvascular reperfusion injury⁹ in patients with ACS. Therefore, the rationale is that inflammatory mechanisms have an important role in the occurrence of AMI^{2,8–14} 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 predictors are sparse^{13,14}.

Interleukin (IL)-18 is a member of the IL-1 family of cytokines and is processed, like IL-1, by caspase 1^{15–16}. Originally, IL-18 was identified as an interferon- γ -inducing factor,¹⁷ stimulating interferon- γ -induction in T lymphocytes and natural killer cells, which have been ascribed a key role in atherosclerotic plaque rupture^{6,18,19}. There is increasing data to demonstrate that IL-18 is a pleiotropic proinflammatory cytokine²⁰ acting in both acquired and innate immunity, and plays a crucial role in the inflammatory cascade²¹. Recent evidence from experimental studies has demonstrated that IL-18 is intimately related to atherosclerotic plaque propagation and instability^{6,22,23}. Additionally, IL-18 has been found to be independently predictive of future coronary events in both coronary disease and healthy subjects^{4,24}. Although 1 previous small study dem-

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Table 1 Baseline Characteristics of Study Patients, and the At-Risk Control and Normal Control Subjects

	Study patients (n=267)	At-risk control (n=30)	Normal control (n=25)	p value [‡]
Age (years) (mean±SD)	60.3±12.3	61.1±10.3	60.6±12.5	0.684
Male gender	80.5% (215)	76.7% (23)	80.0% (20)	0.841
Hypertension	53.6% (143)	50.0% (15)	—	0.711
Diabetes mellitus	31.8% (85)	36.7% (11)	—	0.592
Current smoking	42.7% (114)	46.7% (14)	—	0.677
Hypercholesterolemia	46.1% (123)	43.3% (13)	—	0.776
Previous stroke	7.5% (20)	—	—	
Previous myocardial infarction	7.2% (19)	—	—	
Inflammatory biomarkers*				
hs-CRP (mg/L)	9.0±20.4 ^a	1.5±0.7 ^b	1.1±0.6 ^c	<0.0001
WBC counts (×10 ³ /ml)	10.2±3.4 ^a	6.2±1.3 ^b	6.3±1.3 ^b	<0.0001
IL-18 (pg/ml)	498±511 ^a	155±99 ^b	101±72 ^c	<0.0001
Successful reperfusion [†]	90.3% (241)	—	—	

Data are mean value±SD or % (no.) of patients.

hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cell; IL, interleukin.

*a, b, c indicate significant difference (at 0.05 level) by Wilcoxon's rank sum test with Bonferroni's correction.

[†]Infarct-related artery achieved normal coronary blood flow.

[‡]Continuous data analyzed by Kruskal-Wallis test, and categorical data analyzed by chi-square test.

onstrated that IL-18 was markedly increased and correlated with myocardial injury in patients following AMI;²⁵ 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 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 µg/kg) was administered to patients on presentation in the emergency room, followed by a maintenance infusion of 0.15 µg·kg⁻¹·min⁻¹ for 18–24 h. However, tirofiban therapy was subsequently withheld because it was found not to provide any additional benefit to AMI patients who underwent primary PCI.²⁶ 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.²⁷

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), β-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

Table 2 Comparison of Baseline Characteristics, Laboratory Findings, Angiographic Results, and 30-Day Clinical Outcomes of Patients With High and Low IL-18 Levels Following Acute Myocardial Infarction

	High IL-18 level [†] (n=68)	Low IL-18 level [‡] (n=199)	p value*
Age (years) (mean±SD)	63.1±12.8	59.3±12.0	0.026
Female gender	23.5% (16)	18.1% (36)	0.328
Hypertension	55.9% (38)	52.8% (105)	0.656
Diabetes mellitus	39.7% (27)	29.2% (58)	0.107
Current smoking	52.9% (36)	39.2% (78)	0.048
Hypercholesterolemia	42.7% (29)	47.2% (94)	0.512
Previous myocardial infarction	10.3% (7)	6.0% (12)	0.276
Previous stroke	8.8% (6)	8.0% (16)	0.839
WBC counts (×10 ³ /ml)	11.6±4.6	9.7±2.8	<0.0001
hs-CRP (mg/L)	13.1±23.0	7.6±19.3	0.030
IL-18 (pg/ml)	1,103±705	292±122	<0.0001
Peak level of CK-MB (U/L)	667±525	299±259	<0.0001
Anterior wall infarction	66.2% (45)	46.2% (92)	0.005
Cardiogenic shock	39.7% (27)	7.5% (15)	<0.0001
Advanced CHF (≥NYHA Fc3)	67.6% (46)	7.5% (15)	<0.0001
Multivessel disease	69.1% (47)	42.2% (84)	0.0001
Pre-PCI TIMI flow grade (≥2)	13.2% (9)	26.1% (52)	0.030
Mean reperfusion time (min)	326±164	297±139	0.240
Stenting	84.9% (56)	80.9% (161)	0.612
PercuSurge GuardWire use	39.7% (27)	42.7% (85)	0.664
Tirofiban	11.8% (8)	15.6% (31)	0.442
Successful reperfusion	77.9% (53)	94.5% (188)	<0.0001
LVEF (%)	47.7±10.8	59.6±11.7	<0.0001
30-day mortality	33.8% (23)	1.0% (2)	<0.0001

Data are mean value±SD or % (no.) of patients.

CK, creatine kinase; CHF, congestive heart failure; NYHA Fc, New York Heart Association functional class; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; LVEF, left ventricular ejection fraction. Other abbreviations see in Table 1.

*Continuous data analyzed by Wilcoxon's rank sum test, and categorical data analyzed by chi-square test or Fisher's exact test.

[†]IL-18 level ≥560 pg/ml.

[‡]IL-18 level <560 pg/ml.

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.

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

	OR	95%CI	p value
Age (years) (≥ 70 vs < 70)	2.97	1.63–5.40	0.0004
Female vs male	1.84	0.95–3.55	0.068
With vs without hypertension	0.97	0.56–1.70	0.921
With vs without diabetes mellitus	2.03	1.14–3.61	0.016
With vs without current smoking	1.07	0.61–1.87	0.814
With vs without hypercholesterolemia	0.82	0.47–1.44	0.494
IL-18 (≥ 560 vs < 560)* (pg/ml)	27.61	13.35–57.09	< 0.0001
Peak level of CK-MB (U/L)	1.00	0.99–1.00	< 0.0001
hs-CRP level (mg/L)	0.99	0.98–1.01	0.229
WBC counts ($\times 10^3$ /ml)	0.89	0.83–0.97	0.004
With vs without anterior wall infarction	2.54	1.41–4.57	0.002
With vs without cardiogenic shock	17.98	8.09–39.94	< 0.0001
With vs without multi-vessel disease	2.61	1.46–4.69	0.001
Mean reperfusion (> 240 vs ≤ 240 min)	1.08	0.61–1.91	0.785
Post-procedure TIMI-flow (3 vs ≤ 2)	0.28	0.12–0.65	0.003
LVEF (%) (< 50 vs ≥ 50)	12.59	6.57–24.14	< 0.0001

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 $\geq$ class 3 or 30-day death).

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

	OR	95%CI	p value
IL-18 ≥ 560 (pg/ml)	12.74	5.28–30.75	< 0.0001
LVEF $< 50\%$	6.60	2.67–16.33	< 0.0001
Age (≥ 70 years)	3.47	1.33–9.03	0.011
Cardiogenic shock	12.29	3.86–39.13	< 0.0001

Abbreviations see in Tables 1–3.

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

	OR	95%CI	p value
IL-18 ≥ 560 (pg/ml)	33.0	6.95–156.9	< 0.0001
Cardiogenic shock	6.41	2.17–18.95	0.001

Abbreviations see in Tables 1–3.

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 left ventricular ejection fraction (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 $\leq 50\%$.

Age ≥ 70 years, diabetes mellitus, WBC count, multivessel disease and anterior wall MI were significantly related to an increased incidence of 30-day MACE, whereas successful reperfusion was associated with a decreased 30-day MACE.

Multiple stepwise logistic regression analysis (Table 4) of all significant univariate factors showed that IL-18 level, LVEF $< 50\%$, and cardiogenic shock were the strongest independent predictors of 30-day MACE. Older age (≥ 70 years) was also independently predictive of 30-day MACE. Multiple stepwise logistic regression analysis (Table 5) of all significant univariate factors showed that IL-18 level was the most significant and independent factor associated with 30-day mortality. Although less powerful than the IL-18 level, cardiogenic shock was also independently predictive of 30-day mortality.

Discussion

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^{28–31} 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 cytokine²¹ by inducing IL-1, IL-8,^{16,17} and the expression of adhesion molecules.³² 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.²¹ Surprisingly, in view of the potent inflammatory activities of IL-18,^{6,20,22–24} 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,²⁵ 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^{9,20,25} 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,³³ which supports our suggestion. Additionally, previous studies have clearly shown that an acute elevation of inflammatory mediators occurs following ACS^{2,4,25,33} and another⁹ found that AMI induced cardiac release of cytokines and inflammatory responses. Moreover, an experimental study¹⁰ 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;^{6,22,23} 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.^{13,34–36} Evidence also supports that rapidly and markedly increased circulat-

ing levels of neurohormones or inflammatory cytokines, which in turn elicit overreactive responses systemically, are harmful to AMI patients.^{9,37,38} 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.^{34–36} Moreover, an association between increased circulating cytokines and microvascular reperfusion injury has been identified.^{9,39} Furthermore, cytokines originating from the myocardium or infiltrating inflammatory cells contribute to the raised CRP concentrations observed in patients with AMI.³⁶ Accordingly, our suggestion, based on our findings, is further supported by the findings of these studies.^{9,13,34–36,39}

The most important finding in the present study is that an increased circulating level of IL-18 has been identified as a major independent predictor of 30-MACE and mortality. Recently, inflammatory cytokines were further identified as predictive of untoward clinical outcomes.¹¹ Therefore, our finding strengthens those of another recent study¹¹ and encourages the use of the circulating level of IL-18 as a predictor of clinical outcomes in patients following AMI.

Study Limitations

First, without serial measurement of circulating IL-18 levels, we could not provide information regarding how early the circulating IL-18 elevated and how long the elevation of IL-18 persisted. However, previous studies have demonstrated that the IL-18 level is highly dynamic following AMI, with a marked increase in the early phase of AMI and correlation with myocardial injury.^{25,33} Second, the effects of circulating IL-18 on long-term clinical outcomes were not part of the protocol, so these relationships did not extend beyond the 30-day clinical outcome endpoint.

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.

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