# Levels and Value of Soluble P-Selectin Following Acute Myocardial Infarction: Evaluating the Link between Soluble P-selectin Levels and Recruitment of Circulating White Blood Cells and the Marker for the Rapid Diagnosis of Chest Pain

Cheng-An Chiu, MD; Chiung-Jen Wu, MD; Cheng-Hsu Yang, MD; Chih-Yuan Fang, MD; Yuan-Kai Hsieh, MD; Chi-Ling Hang, MD; Wei-Chin Hung, MD; Chien-Jen Chen, MD; Shyh-Ming Chen, MD; Teng-Hung Yu, MD; Kuo-Ho Yeh, MD; Morgan Fu, MD; Hon-Kan Yip, MD

**Background:** Platelet activation that results from coronary plaque rupture is important in the pathogenesis of acute myocardial infarction (AMI). Soluble p-selectin (sP-selectin) is crucial in modulating leukocyte adhesion to both platelets and endothelial cells during inflammatory response and thrombus formation. We hypothesized that sP-selectin, an index of both platelet activation and acute inflammation, rapidly increases and modulates the recruitment of circulating white blood cells (WBC) in patients following AMI.

**Methods:** We conducted a prospective cohort study of 142 consecutive patients with ST-segment elevated AMI of onset < 12 h who were undergoing primary percutaneous coronary intervention. Blood samples for plasma levels of sP-selectin were obtained in the catheterization laboratory before coronary angiography was performed. The plasma levels of sP-selectin were also measured in 30 risk control subjects and 20 healthy control subjects.

**Results:** The plasma level of sP-selectin and the circulating WBC count were significantly higher in patients with AMI than in either the risk control or healthy subjects (all of $p$ values < 0.0001). Additionally, repeated measures of ANOVA demonstrated that there were no significant differences in plasma levels of sP-selectin ($p > 0.10$) in three intervals from the start of chest pain to blood sample collection (< 180 min, ≥ 180 < 360, and ≥ 360 < 720) following AMI. Correlation analysis demonstrated that the increase in the plasma level of sP-selectin was significantly related to the circulating WBC count ($r = 0.248$, $p = 0.003$).

**Conclusions:** sP-selectin was markedly elevated in an early phase of AMI. sP-selectin may be involved in modulating the recruitment of circulating WBC during AMI. These findings raise the need for a prospective investigation of sP-selectin as a potential reliable clinical tool for rapidly diagnosing AMI.

*(Chang Gung Med J 2005;28:699-707)*

**Key words: sP-selectin, WBC count, acute myocardial infarction.**

From the Division of Cardiology, Chang Gung Memorial Hospital, Kaohsiung.
Received: Feb. 23, 2005; Accepted: Aug. 9, 2005
Correspondence to: Dr. Hon-Kan Yip, Division of Cardiology, Chang Gung Memorial Hospital. 123, Dabi Road, Niaosung Shiang, Kaohsiung, Taiwan 833, R.O.C. Tel.: 886-7-7317123; Fax: 886-7-7322402; Email: tang@adm.cgmh.org.tw

Acute myocardial infarction (AMI) is the leading cause of death in patients hospitalized with cardiovascular disease in industrialized societies.[1] The underlying cellular and molecular mechanisms of disease initiation and progression are quite complex.[2-4] An early event in vessel injury is the adhesion of platelets and leukocytes to the damaged arterial wall.[5,6] Growing evidence has demonstrated that an acute inflammatory process which results in platelet aggregation and leukocyte adhesion to the endothelium in the coronary circulation plays a crucial role in thrombus formation[3,7] and subsequently in the development of AMI.[3] P-selectin, a cellular adhesion molecule of platelets and endothelial cells stored in both the α-granules of platelets and in the Weibel-Palade bodies of endothelial cells,[8,9] is rapidly expressed on the surface of activated platelets and endothelial cells.[10,11] It is involved in mediating platelets and the rolling of leukocytes on activated endothelial cells[12,13] as well as in interactions of activated platelets with leukocytes.[14] Other studies also demonstrated that the size of the aggregated platelets and the immobilization of platelets on the clots depend on P-selectin.[7,15]

Soluble P-selectin (sP-selectin), is a form of P-selectin which can be detected in plasma and represents a marker of platelet activation. Until recently, little data on plasma levels of sP-selectin were available in patients with acute coronary syndromes.[16-18] Only two recent studies[16,17] have investigated the plasma levels of sP-selectin following AMI. They demonstrated that the levels of sP-selectin are significantly higher in patients in the clinical setting of AMI who are undergoing thrombolytic therapy than in healthy control subjects. However, the sample sizes of these two studies were very small. Furthermore, while leukocyte accumulation plays an important role in promoting fibrin deposition,[7] the relationship between increased plasma levels of sP-selectin and the recruitment of circulating WBC in patients with AMI remains undetermined. Whether sP-selectin can be utilized as a marker for an early, rapid diagnosis of AMI is also uncertain. Accordingly, the purpose of this study was to investigate the levels of plasma sP-selectin and the link between plasma sP-selectin levels and the circulating WBC count in patients with AMI who were undergoing primary percutaneous coronary intervention (PCI). Plasma sP-selectin may thus become a useful tool in daily clinical practice for the early, rapid diagnosis of AMI.

## METHODS

### Study population and inclusion criteria

In our hospital, all patients with AMI were considered eligible for primary PCI. For the purpose of this study, the plasma levels of sP-selectin and the WBC counts of all patients who underwent primary PCI were prospectively evaluated. Blood samples were drawn after vascular puncture and before coronary angiography in the cardiac catheterization laboratory. Patients with a history of renal insufficiency (creatinine > 1.5 mg/dL), malignancy, febrile disorders, acute or chronic inflammatory disease at the beginning of the study, a history of recent infection, gross hemolysis of the blood sample, or immunosuppressive therapy were excluded to ensure that other variables would not influence the plasma levels of sP-selectin and the WBC counts. Patients were also excluded if a fever (body temperature > 37.50°C) was observed in the emergency room. Between July 2002 and March 2003, 165 consecutive patients of any age who presented with AMI and were undergoing primary PCI in our hospital were prospectively investigated and recruited. Twenty-three (13.9%) of the 165 patients were subsequently excluded due to fever (5 patients), infection (3 patients), malignancy (2 patients), steroid use (2 patients), gross hemolysis (5 patients), or impaired renal function (6 patients). Therefore, the remaining 142 patients constituted the study population.

Thirty subjects who had risk factors of coronary artery disease and were treated in the outpatient department were matched with respect to age, gender, hypertension, diabetes mellitus, current smoking and hypercholesterolemia and served as risk factor control subjects. Twenty healthy age- and gender-matched volunteers were also investigated. Informed consent was obtained from all subjects. The Institutional Review Committee on Human Research in our institution approved the protocol.

### Procedure and protocol

A transradial artery approach using a 6 F arterial sheath was routinely applied for AMI in our hospital unless Allen's test was positive. A 6 F Kimny Miniradi (Boston Scientific, Scimed, Inc. Maple

Grove, MN. USA) was used for both diagnosis and primary PCI.

At the beginning of the study, tirofiban therapy (loading dosage of 20 μg/kg of body weight) was administered to patients upon presentation in the emergency room, followed by a maintenance infusion of 0.15 μg/min for 18 to 24 hours. However, tirofiban therapy was subsequently withdrawn because this therapy was not found to provide any additional benefits to patients with AMI who underwent primary PCI.[19] Therefore, only 31 patients received tirofiban therapy in this study.

Clopidogrel (loading dose of 400 mg after stenting then 75 mg daily) was given for at least four weeks to patients who underwent primary stenting and aspirin (100 mg orally once a day) was administered to each patient indefinitely.

**Blood sampling and laboratory investigations**

Blood samples were obtained once from both healthy volunteers in an examination at a health clinic and from risk-control subjects in the outpatient department. White blood cells were counted and biochemical measurements made using standard laboratory methods.

**Enzyme-linked immunosorbent assay for soluble P-selectin**

After vascular puncture, 5 cc. of blood was drawn into an evacuated tube that contained $K_3$ ethylenediamine tetra acetic acid (vacutainer from Becton Dickinson; Franklin Lakes, NJ, USA). If the blood sample exhibited gross hemolysis, it was discarded. Other blood samples were mixed immediately by gentle inversion and centrifuged (model 5400; Kubota Corp; Tokyo, Japan) at 3000 revolutions per minute for 10 minutes at room temperature. All aliquots of the samples were stored at -800°C until the assay was performed.

The concentration of sP-selectin was measured using a commercially available solid-phase sandwich enzyme-linked immunosorbent assay kit (R and D Systems; Minneapolis, MN, USA). The samples were processed according to the manufacturer's instructions. The concentration of recombinant human sP-selectin was reconstituted as standards at various concentrations; 1.0 mL distilled water was added to each standard immediately before use. The sP-selectin control was reconstituted immediately before use by adding 500 μL of distilled water. The sP-selectin control was then diluted 20-fold in the sample diluent prior to assay. A sP-selectin microplate which contained 96 wells was coated with murine monoclonal antibody to human sP-selectin. The procedure was performed as follows: First, 100 μL of sP-selectin standard, sP-selectin control or sample was added to each well; then 100 μL of sP-selectin conjugate (horseradish peroxidase) was added to each well and incubated for 1 hour at room temperature. The unbound materials were then aspirated and washed three times. Substrate (tetramethylbenzidine, which is specific to the enzyme) 100 μL was then added to each well and incubated for 15 minutes at room temperature. Finally, 100 μL of stop solution was added to each well.

The reaction product was measured within 30 minutes using a microplate reader (MRX; Dynex Technologies, Inc.; Chantilly, VA, USA) and the absorbance was read at 450 nm with a correction wavelength of 630 nm. A standard curve was plotted using the mean absorbance values of the included sP-selectin standards and the sP-selectin concentrations in all unknown plasma samples were then calculated by linear regression. The assay was sufficiently sensitive to detect less than 0.5 ng/ml of P-selectin according to the manufacturer of the assay kits. The intra-individual variabilities of the sP-sectin levels in study patients, risk-control subjects and healthy subjects were assessed. The mean intra-assay coefficients of variance were 5.10%, 4.71% and 4.34%, respectively.

**Definitions and data collection**

AMI was defined by the presence of typical chest pain for more than 30 minutes with ST-segment elevation >1 mm in two consecutive precordial or inferior leads. The body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters ($kg/m^2$). Unsuccessful reperfusion was defined as post-PCI thrombolysis in myocardial infarction (TIMI) flow ≤ 2. Failure of microvasculature reperfusion was defined as post-PCI myocardial blush (MB) grade ≤ 1.[20]

Detailed in-hospital and follow-up data were obtained including age, gender, coronary risk factors, Killip score on admission, pre-infarction angina, BMI, body temperature on admission, white blood cell count, creatinine level, angiographic findings

and number of diseased vessels. These data were collected prospectively and entered into a computerized database.

**Statistical analysis**

Categorical variables were compared using the chi-square test or Fischer's exact test. Continuous variables were compared using the *t* test. Continuous variables among the three groups were compared using repeated measures of ANOVA and Scheffe's post hoc multiple comparison procedure was used if significant differences existed among groups. Statistical analysis was performed using SAS statistical software for Windows version 8.2 (SAS Institute, Cary, NC, USA). A probability $p$ value $< 0.05$ was considered statistically significant.

## RESULTS

**Baseline characteristics of study patients, angina patients and healthy control subjects (Table 1)**

Table 1 depicts the baseline characteristics of study patients, risk control subjects and normal control subjects. The three groups did not differ significantly with regard to age, diabetes mellitus, hypercholesterolemia, previous stroke or previous MI. However, the study patients included proportionally more males than either the risk control or healthy control subjects. The incidences of hypertension and current smoking were significantly higher in the study patients than in the risk control subjects. Moreover, the plasma levels of sP-selectin and the circulating WBC counts were significantly higher in study patients than in either the risk control or healthy control subjects. However, a significantly lower percentage of study patients than risk control subjects used statins for hypercholesterolemia.

**Baseline variables, laboratory findings and angiographic results relevant to plasma levels of soluble P-selectin in study patients (Table 2 and Fig. 1)**

The results in Table 2 demonstrate that the baseline variables, including advanced age (≥ 70 yrs), gender, smoking, hypertension, hypercholesterolemia, previous MI, old stroke, and location of infarction, were not significantly associated with increases in the plasma level of sP-selectin. Additionally, multi-vessel disease, pre-PCI TIMI flow and unsuccessful reperfusion was not significantly associated with increases in sP-selectin. Nevertheless, diabetes mellitus, no tirofiban therapy, post-PCI MB grade ≤ 1 and death within 30 days had tendencies toward statistically significant relationships with increased plasma levels of sP-selectin. Correlation analysis demonstrated that the increase in the plasma levels of sP-selectin was significantly

**Table 1.** Baseline Characteristics of Study Patients, Risk Control and Healthy Control Subjects*

| Variables | Study Patients (n = 142) | Risk Controls (n = 30) | Healthy Controls (n = 20) | *p* |
|---|---|---|---|---|
| Age (yrs) (mean ± SD) | 61.5 ± 12.0 | 65.3 ± 8.9 | 59.1 ± 8.0 | 0.135 |
| Male gender | 82.4% (117) | 56.7% (17) | 50.0% (10) | 0.0003 |
| Hypertension | 53.5% (76) | 76.7% (23) | – | 0.020 |
| Diabetes mellitus | 35.9% (51) | 30.0% (9) | – | 0.537 |
| Current smoking | 55.6% (79) | 30.0% (9) | – | 0.011 |
| Hypercholesterolemia | 46.5% (66) | 43.3% (13) | – | 0.753 |
| Previous MI | 6.3% (9) | 16.7% (5) | – | 0.073 |
| Previous stroke | 10.6% (15) | 3.3% (1) | – | 0.311 |
| WBC counts (x $10^3$/mL)† | 10.76 ± 3.43[a] | 6.11 ± 1.52[b] | 5.02 ± 0.97[b] | < 0.0001 |
| Simvastatin treatment | 5.6% (8) | 56.7% (17) | – | < 0.0001 |
| Tirofiban therapy | 21.8% (31) | – | – | – |
| PercuSurge device use | 31.7% (45) | – | – | – |
| *Multiple vessel disease | – | – | – | – |
| sP-selectin (ng/ml)† | 68.3 ± 22.9[a] | 33.7 ± 15.6[b] | 29.5 ± 6.3[b] | < 0.0001 |

**Abbreviations:** MI: myocardial infarction; WBC: white blood cell.

* Values are given as mean value ± SD or No. (%), unless otherwise indicated.

† Means with different letters (a, b) indicate significant difference (at 0.05 level) by Scheffe's multiple comparison procedure.

**Table 2.** Univariate Analysis of Baseline Characteristics and Angiographic Features Relevant to Plasma Levels of Soluble P-Selectin*

| Variables | Soluble P-selectin (ng/ml) | *p* |
|---|---|---|
| Age (70 versus < 70 yrs) | 66.1 ± 23.5 vs. 69.2 ± 22.7 | 0.458 |
| Men vs. women | 68.6 ± 23.8 vs. 76.2 18.8 | 0.786 |
| DM vs. non-DM | 73.2 ± 21.9 vs. 65.6 ± 23.1 | 0.055 |
| Current smoker vs. non-smoker | 71.0 ± 23.1 vs. 65.0 ± 22.4 | 0.124 |
| With vs. without H/T | 65.7 ± 23.1 vs. 71.3 ± 22.5 | 0.143 |
| With vs. without hypercholesterolemia | 70.2 ± 25.3 vs. 66.7 ± 20.6 | 0.361 |
| With vs. without previous MI | 65.6 ± 25.2 vs. 68.5 ± 22.0 | 0.813 |
| With vs. without previous stroke | 73.1 ± 18.2 vs. 67.7 ± 23.4 | 0.393 |
| Anterior vs. non-anterior infarction | 68.4 ± 23.6 vs. 68.2 ± 22.3 | 0.974 |
| Cardiogenic vs. non-cardiogenic shock | 72.3 ± 19.8 vs. 67.6 ± 23.4 | 0.402 |
| Multi-vessel vs. single vessel disease | 71.1 ± 24.2 vs. 65.2 ± 21.2 | 0.126 |
| WBC counts (x $10^3$/mL): < 10 vs. ≥ 10 | 63.0 ± 24.3 vs. 72.4 ± 21.0 | 0.014 |
| AMI duration < 360 vs. ≥ 360 minutes | 70.3 ± 23.4 vs. 64.1 ± 24.5 | 0.132 |
| Pre-TIMI flow ( 1 vs. 2) | 67.5 ± 22.4 vs. 70.2 ± 24.2 | 0.522 |
| With vs. without tirofiban therapy | 66.5 ± 24.4 vs. 73.1 ± 17.8 | 0.078 |
| 30-day outcomes (death vs. survival) | 77.8 ± 15.5 vs. 67.1 ± 23.5 | 0.079 |
| Post-PCI TIMI flow (3 vs. ≤ 2) | 67.9 ± 23.2 vs. 71.4 ± 21.0 | 0.569 |
| Post-PCI MB grade (≥ 2 vs. ≤ 1) | 67.0 ± 22.3 vs. 76.1 ± 25.2 | 0.062 |

**Abbreviations:** AMI: acute myocardial infarction; DM: diabetes mellitus; H/T: hypertension; MB: myocardial blush; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction; WBC: white blood cell.

* Values are given as mean value ± SD, unless otherwise indicated; the *t* test was used for analysis.

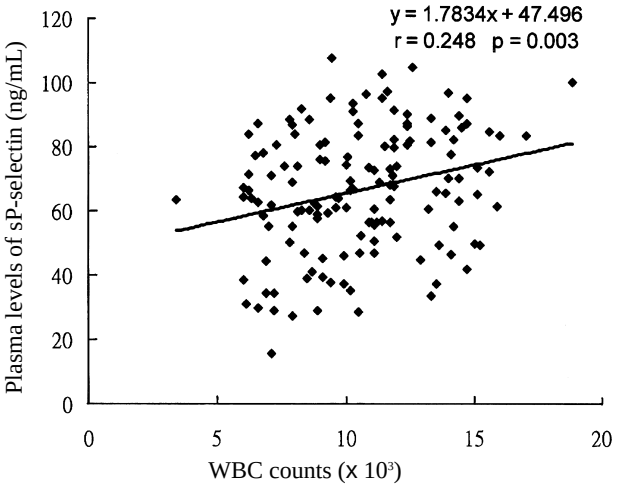


**Fig. 1** Correlation between plasma levels of soluble P-selectin (sP-selectin) and white blood cell counts in patients following acute myocardial infarction.

related directly to the increase in the circulating WBC count (r = 0.248, $p = 0.003$) (Fig. 1).

### Serial changes in plasma levels of soluble P-selectin

Repeated measures of ANOVA demonstrated an absence of serial changes in plasma levels of sP-selectin (65.4 ± 20.1 vs. 68.8 ± 18.9 vs. 63.0 ± 19.3, $p > 0.10$) in three intervals from the start of chest pain to blood sample collection (< 180 min, ≥ 180 < 360, and ≥ 360 < 720) following AMI. However, the plasma levels of sP-selectin in patients after AMI in each of these three intervals was significantly higher than those in the healthy control subjects and risk control subjects ($p < 0.0001$) (Fig. 2).

## DISCUSSION

### Plasma levels of soluble P-selectin in patients following AMI

Previous studies demonstrated that plasma levels of sP-selectin markedly increase in patients following AMI.[16,17] However, the value and clinical implication of sP-selectin have not been fully clari-

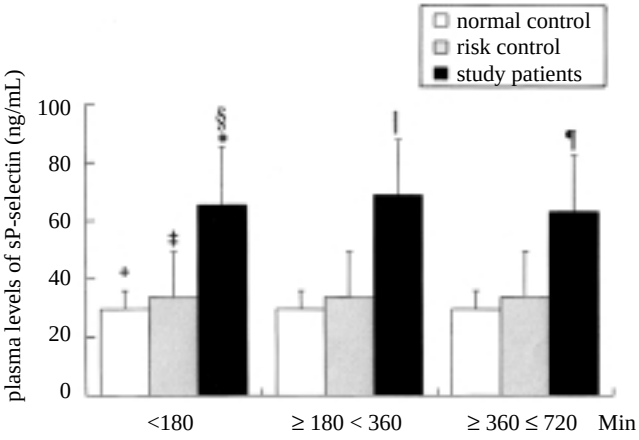


**Fig. 2** Serial changes in plasma levels of sP-selectin. Blank bars and gray bars represent the plasma levels of sP-selectin of healthy control subjects and risk control subjects. Black bars represent the plasma levels of sP-selectin of study patients at three intervals from the start of chest pain to blood sample collection. *(study patients) vs. † (healthy control) and ‡ (risk control), all *p* values < 0.0001. † (healthy control) vs. ‡ (risk control), $p > 0.10$. Plasma level of sP-selectin at three time intervals after AMI: §(< 180 min) vs. ‖(≥ 180 < 360 min.) vs. ¶ (≥ 360 ≤ 720 min), all *p* values > 0.10.

fied because of the small sample sizes and the limited number of studies.[16-18] The present study is the largest cohort study which has demonstrated that the plasma level of sP-selectin is significantly higher in study patients than in healthy control or risk control subjects. The results of this study support the findings of previous studies[16,17] and provide additional information for future clinical research into AMI.

**Value and clinical implications of soluble P-selectin in patients following AMI**

Previous studies demonstrated that P-selectin, which is stored both in the α-granules of platelets and in the Weibel-Palade bodies of endothelial cells in the preformed stage,[8,9] is rapidly mobilized to the cell surface within minutes in response to various inflammatory and prothrombotic stimuli.[10,11,21] Both the enzymatic cleavage of expressed P-selectin and the alternative splicing of P-selectin messenger ribonucleic acid give rise to a soluble form of P-selectin (sP-selectin) which is detectable in the peripheral blood.[22] This study demonstrated that the plasma level of sP-selectin in patients with AMI < 180 minutes is also significantly higher than that in either healthy control or risk control subjects. Furthermore, plasma levels of sP-selectin exhibited no significant serial changes within 12 hours of AMI. Accordingly, we suggest that sP-selectin is rapidly expressed and rapidly released from activated platelets and endothelial cells into the circulation following AMI. Our findings confirm previous reports[10,11,21,22] and extend the findings of these studies[10,11,21,22] by showing that sP-selectin may be utilized in the emergency room as an early diagnostic tool for acute coronary syndromes. Another investigation offered the same suggestion.[23]

**Implications of link between increased plasma soluble P-selectin and white blood cell count after AMI**

This investigation reveals that the WBC count is significantly correlated to increased plasma levels of sP-selectin. We suggest that in addition to the stress relationship with severe chest pain, sP-selectin may also participate in the recruitment of WBC in the circulation following AMI. An animal model study demonstrated that accumulation of leukocytes in the thrombus, which is mediated by P-selectin, promotes the deposition of fibrin.[7] Another study suggested that sP-selectin may be involved biologically in modulating leukocyte recruitment or thrombus growth.[24] Our suggestion is based on our clinical observations and is supported by experimental studies.[7,24] In the present study, we found the correlation coefficient ($r = 0.248$) was relatively small. We suggest that this may be due to the effect of the sample size or other factor(s) which play a more important role than sP-selectin in the recruitment of circulating WBC.

We hypothesized that the elevated plasma level of sP-selectin is strongly associated with an increased incidence of unsuccessful reperfusion of the microvasculature (MB grade ≤ 1) in infarct-related vessels following primary PCI. This study interestingly found no significant difference between the plasma levels of sP-selectin in post-PCI TIMI-3 flow and those in ≤ TIMI-2 flow. However, a tendency toward a statistically significant difference in the plasma levels of sP-selectin was found between post-PCI MB grade ≥ 2 and MB grade ≤ 1. These findings have two reasonable explanations. First, the synergistic effect of platelets, P-selectin and accumulated leukocytes on thrombus formation which prevents coronary blood flow may extend beyond the epicardial vessels and act primarily in the microvasculature during the primary PCI procedure., During this procedure, large thrombi which have formed in the epicardial vessels are crushed into small thrombi either by the balloon or the stent. These small thrombi are subsequently embolized distally and plug the microvasculature. This explains why the plasma levels of sP-selectin did not differ significantly between patients with successful and unsuccessful reperfusion of the epicardial vessels. whereas there was a tendency toward a statistically significant difference in plasma levels of sP-selectin between patients with successful and failed reperfusion of the microvasculature. Second, we recently demonstrated that the PercuSurge device can prevent distal embolization and increase the integrity of the microvasculature during primary PCI.[25] In the present study, over one-third of our patients had received combined therapy with primary PCI and the PercuSurge device. Hence, we posit that this mechanical device suppresses the synergistic effect of platelets, P-selectin and accumulated leukocytes which leads to unsuccessful reperfusion of the microvasculature. A previous study suggested that leukocytes act as cofactors

in coagulation.[24] Other studies[7,15] have shown that leukocyte accumulation is mediated by P-selectin on adherent platelets and that P-selectin expression on platelets determines the size and stability of the aggregation of platelets. These studies[7,15,24] therefore support the hypothesis based on our clinical observations.

A previous study showed that the activation of glycoprotein IIb/IIIa is maximal within the first 10 seconds of platelet aggregation and that p-selectin is maximally expressed 10 minutes after platelet activation.[15] Therefore, sP-selectin represents a marker of platelet activation.[26] In the present study, we found that tirofiban had only a tendency toward a statistically significant difference in suppression of sP-selectin expression. This finding could partially explain why tirofiban did not provide additional clinical benefits when administered in conjugation with primary PCI.[19]

This investigation had several limitations. First, a rather larger range of standard deviation (SD) of plasma levels of sP-selectin was observed, indicating that the patients exhibited substantial interindividual variability in the sP-selectin level. Therefore, limitation on the sensitivity of this biomarker for the early diagnosis of chest pain in the emergency room should be kept in mind. Second, the plasma level of sP-selectin was not strongly associated with 30-day mortality in this study, perhaps because sP-selectin was shed from activated platelets and endothelial cells rather than from necrotic myocardium which usually linearly correlates with adverse clinical outcomes. Third, the lack of measurement of time courses of plasma levels of sP-selectin in individual patients for comparison prevents ruling out the possibility that serial changes of this biomarker in plasma levels occur in each patient after AMI.

In conclusion, this study demonstrates that sP-selectin, a marker of platelet and endothelial activation, is rapidly and substantially increased without significant serial changes in the circulation following AMI. This biomarker may play an important role in the recruitment of circulating leukocytes after AMI. These findings raise the need for prospective research into whether the plasma level of sP-selectin could be a reliable and applicable clinical tool for the rapid diagnosis of acute coronary syndromes.

## REFERENCES

1. American Heart Association – 2000 Heart and Stroke Statistical Update. Dallas, TX: American Heart Association, 2000.
2. Hansson GK. Immune and inflammatory mechanisms in the development of atherosclerosis. Br Heart J 1993;69: S38-S42.
3. van der Wall AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994;89:36-44.
4. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999;340:115-26.
5. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. New Engl J Med 1992;326:242-50.
6. Ross R. The pathogenesis of atherosclerosis: a prospective for the 1990s. Nature 1993;362:802-9.
7. Palabrica T, Lobb R, Furie BC, Aronovitz M, Benjamin C, Hsu YM, Sajer SA, Furie B. Leukocyte accumulation promoting fibrin deposition is mediated in vivo by P-selectin on adherent platelets. Nature 1992;359:848-51.
8. Wagner DD. The Weibel-Palade body: the storage granule for von Willebrand factor and p-selectin. Throm Haemost 1993;70:1-5.
9. McEver RP, Beckstead JH, Moore KL, Marshall-Carlson L, Bainton DF. GMP-140, a platelet α-glanule membrane protein, is also synthesized by vascular endothelial cells and is localized in Weibel-Palade bodies. J Clin Invest 1989;84:92-9.
10. Berman CL, Yeo EL, Wencel-Drake JD, Furie BC, Ginberg MH, Furie B. A platelet alpha-granule membrane protein that is associated with the plasma membrane after activation: characterization and subcellular localization of platelet activation-dependent granule-external membrane protein. J Clin Invest 1986;78:130-7.
11. Carlos TM, Harlan JM. Leukocyte-endothelial adhesion molecules. Blood 1994;84:2068-101.
12. Hsu SL, Berman CL, Furie BC, Augus D, Furie B. A platelet membrane protein expressed during platelet activation and secretion: studies using a monoclonal antibody specific for thrombin-activated platelets. J Biol Chem 1984;259:9121-6.
13. Frenette PS, Johnson RC, Hynes RO, Wagner DD. Platelets roll on stimulated endothelium in vivo: an interaction mediated by endothelial P-selectin. Proc Natl Acad Sci USA 1995;92:7450-4.
14. Gamble JR, Skinner MP, Berndt MC, Vadas MA. Prevention of activated neutrophil adhesion to endothelium by soluble adhesion protein GMP 140. Science 1990;249:414-7.

15. Merten M, Thiagarajan P. P-selectin expression on platelets determines size and stability of platelet aggregates. Circulation 2000;102:1931-6.
16. Shimomura H, Ogawa H, Arai H, Arai H, Moriyama Y, Takazoe K, Hirai N, Kaikita K, Hirashima O, Misumi K, Soejima H, Nishiyama K, Yasue H. Serial changes in plasma levels of soluble P-selectin in patients with acute myocardial infarction. Am J Cardiol 1998;81:397-400.
17. Gurbel PA, O'Connor CM, Dalesandro MR, Serebruany VL. Relation of soluble and platelet P-selectin to early outcome in patients with acute myocardial infarction after thrombolytic therapy. Am J Cardiol 2001;87:774-7.
18. Murphy RT, Foley B, Mulvihill N, Crean P, Walsh MJ. Impact of preexisting statin use on adhesion molecule expression in patients presenting with acute coronary syndromes. Am J Cardiol 2001;87:446-8.
19. Yip HK, Wu CJ, Chang HW, Hsieh YK, Fang CY, Chen SM, Chen MC. Impact of tirofiban on angiographic morphologic features of high-burden thrombus formation during direct percutaneous coronary intervention and short-term outcomes. Chest 2003;124:962-8.
20. van't Hof AWJ, Liem A, Suryapranata H, Hoorntje JCA, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Circulation 1998;97:2302-6.
21. Furie B, Furie BC. The molecular basis of platelet and endothelial cell interaction with neutrophils and monocytes: role of P-selectin and the P-selectin ligand, PSGL-1. Thromb Haemost 1995;74:224-7.
22. Ishiwata N, Takio K, Katayama M, Watanabe K, Titani K, Ikeda Y, Handa M. Alternative spliced isoform of P-selectin is present in vivo as a soluble molecule. J Biol Chem 1994;269:23708-5.
23. Gurbel PA, Kereiakes DJ, Dalesandro MR, Bahr RD, O'Connor CM, Serabraunary VL. Role of soluble and platelet bound P-selectin in discriminating cardiac from non cardiac chest pain presentation in the emergency department. Am Heart J 2000;139:320-8.
24. Berger G, Hartwell DW, Wangner DD. P-selectin and platelet clearance. Blood 1998;92:4446-52.
25. Yip HK, Wu CJ, Chang HW, Fang CY, Yang CH, Chen SM, Hung WC, Chen CJ, Cheng CI, Hsieh YK. Effect of PercuSurge GuardWire device on the integrity of microvasculature and clinical outcomes during primary transradial coronary intervention in acute myocardial infarction. Am J Cardiol 2003;92:1331-5.
26. Kawabata K, Nagake Y, Shikata K, Fukuda S, Nakazono H, Takahashi M, Ichikawa H, Makino H. Soluble P-selectin is released from activated platelets in vivo during hemodialysis. Nephron 1998;78:148-55.

# 由血小板分泌可溶性黏著因子 sP-Selectin 在急性心肌梗塞病人的血中濃度與臨床價值

邱正安 吳炯仁 楊正旭 方志元 謝元凱 洪志凌 洪尉欽 陳建仁 陳世明
尤登弘 葉國和 傅懋洋 葉漢根

**背 景：** 冠狀動脈斑塊破裂引起之血小板活化在急性心肌梗塞的致病原因中佔有重要的地位。在發炎反應與血栓形成時，由血小板分泌可溶性黏著因子 (soluble P-Selectin) 在白血球附著到血小板及內皮細胞的調節上很重要。我們假設可溶性黏著因子是血小板活化與急性發炎的指標，在急性心肌梗塞後會快速增加，並且調節白血球在循環中的補充(recruitment)。

**方 法：** 我們進行一項前瞻性的研究，包含 142 位在 12 小時內發生 ST 波段上升之急性心肌梗塞並進行緊急心導管手術 (primary coronary angioplasty) 的病人。測量血中可溶性黏著因子的血液樣本(blood sampling) 都在心導管手術前取得。另外，也取得了 30 位危險因子控制組(risk control subjects) 與 20 位正常控制組 (healthy control subjects) 的受試者血中可溶性黏著因子的濃度。

**結 果：** 結果發現，急性心肌梗塞病人血中可溶性黏著因子與白血球的數目，在統計學上有非常顯著差異的高於其他兩組控制組 ($p$ 值 < 0.0001)。除此之外，在急性心肌梗塞後，repeated measures of ANOVA 統計法證明了從胸痛算起的 3 段不同時間間隔 (< 180 分 vs. ≥ 180 < 360, vs. ≥ 360 < 720) 所得之可溶性黏著因子值並無顯著差異 ($p$ 值 > 0.10)。在相關性的分析中，顯示出可溶性黏著因子的增加與白血球數目的補充有明顯的相關性 (r = 0.248, $p$ = 0.003)。

**結 論：** 可溶性黏著因子在急性心肌梗塞的很早期會顯著的升高。在急性心肌梗塞時，可溶性黏著因子可能在調節白血球的補充上，佔有重要的地位。爲了早期診斷急性心肌梗塞，本次研究對於可溶性黏著因子是否爲可信賴之臨床診斷工具，提升了進一步研究的必要性。

(長庚醫誌 2005;28:699-707)

**關鍵字：** 可溶性黏著因子血中濃度，白血球數目，急性心肌梗塞。

長庚紀念醫院　高雄院區　心臟內科
受文日期：民國94年2月23日；接受刊載：民國94年8月9日
通訊作者：葉漢根醫師，長庚紀念醫院　心臟內科。高雄縣833鳥松鄉大埤路123號。Tel.: (07)7317123; Fax: (07)7322402; E-mail: tang@adm.cgmh.org.tw