Plasma Procalcitonin in Sepsis and Organ Failure

H Yukioka,*MD, G Yoshida,**MD, S Kurita,**MD, N Kato,***MD

Abstract

***Introduction**: Because the use of procalcitonin (PCT) as a marker of bacterial infection has been advocated, this study was carried out to determine the usefulness of plasma PCT in the early diagnosis and differentiation of patients with non-infectious systemic inflammatory response syndrome (SIRS) from those with sepsis, and the relationship between plasma PCT level and severity of organ failure. **Materials and Methods**: Thirty-five patients with non-septic SIRS (n = 16), sepsis (n = 7) or septic shock (n = 12) were included in this study. PCT and C-reactive protein (CRP) levels were measured and sepsis-related organ failure assessment (SOFA) score was calculated for these patients. Plasma PCT was measured by immunoluminometric assay. **Results**: The median (minimum, maximum) plasma PCT levels were 0.6 (0.1, 3.4) ng/mL in non-septic SIRS, 5.4 (0.9, 47.7) ng/mL in sepsis and 73.4 (9.6, 824.1) ng/mL in septic shock, and significant differences existed in plasma PCT levels among the three groups. The median (minimum, maximum) CRP levels were 13.8 (0.3, 48.8) mg/dL in non-septic SIRS, 23.3 (1.4, 26.6) mg/dL in sepsis and 17.4 (2.2, 34.1) mg/dL in septic shock, without significant differences among the three groups. A good correlation was found between plasma PCT level and SOFA score (r_s = 0.766, P <0.0001), although no correlation was found between CRP level and SOFA score. **Conclusions**: CRP is increased by inflammatory disease as well as infection and is therefore not a good indicator of infection in patients with severe SIRS. On the other hand, PCT is a good indicator of severity of sepsis and organ failure in patients with severe SIRS since PCT levels correlated with sepsis and SOFA scores. PCT level is useful for diagnosis of sepsis and as an indicator of severity of organ failure in patients with SIRS.*

***Ann Acad Med Singapore* 2001; 30:528-31**

Key words: C-reactive protein, Septic shock, SOFA score, Systemic inflammatory response syndrome

Introduction

Although severe infection and sepsis are associated with high morbidity and mortality in the intensive care unit (ICU), the classification of severity or definition of sepsis as a syndrome is difficult. Traditional markers of infection such as body temperature and white blood cell count are unreliable and often misleading, since they are markers of systemic inflammation which may be non-infectious in origin and non-specific and non-sensitive for sepsis.

C-reactive protein (CRP) is an acute-phase protein produced by the liver in response to tissue injury or infection. It has been recently shown that plasma CRP level is a good indicator of sepsis and superior to both body temperature and white blood cell count in this respect.[1] On the other hand, definite correlation between infection and CRP change has not yet been documented.

Procalcitonin (PCT) is a precursor of calcitonin in humans, and is a 13-kDa peptide produced under physiological condition in the thyroid glands.[2] In severe infection, PCT is produced outside the thyroid gland.[3] Although the site of PCT production in sepsis is unknown, it may be the macrophages or the liver.[4,5] It has been shown that PCT level increases markedly following severe bacterial infection and can differentiate between infectious and non-infectious systemic inflammation.[6,7] In addition, PCT level increases slightly in patients with viral infections or local infections without sepsis.[3,8]

This study was designed to compare the usefulness of plasma PCT and CRP in early diagnosis and differentiation of patients with non-septic systemic inflammatory response syndrome (SIRS) from those with sepsis, and to determine the relationship between plasma PCT or CRP level and severity of organ failure.

Materials and Methods

The study included 35 adult patients with SIRS admitted to the ICU at the Osaka City University Hospital in Osaka. The patients were sequentially enrolled. The patients were

* *Associate Professor*
** *Research Associate*
*** *Lecturer*
Division of Critical Care Medicine
Osaka City University, Medical School, Osaka, Japan
Address for Reprints: Dr Hidekazu Yukioka, Division of Critical Care Medicine, Osaka City University, Medical School, 1-5-7 Asahi-machi, Abeno-ku, Osaka 545-8586, Japan.

diagnosed as having SIRS (non-septic SIRS), sepsis, or septic shock based on the guidelines of the American College of Chest Physicians/Society of Critical Care Medicine.[9] From all patients in the sepsis group or septic shock group, bacteria or fungi were isolated from blood cultures or in local cultures taken from the lung or the peritoneum. Patients were diagnosed with non-septic SIRS based on the absence of organisms isolated from blood, lung, peritoneum and urine. If diagnosis of non-septic SIRS, sepsis or septic shock was difficult, patients were excluded from the study.

Plasma samples were collected and stored at –20°C on the day of diagnosis of patients with non-septic SIRS, sepsis or septic shock and thereafter 0 to 5 times during the next 2 weeks for measurement of PCT and CRP concentrations. Determination of PCT and CRP concentrations was performed when the patients had already been allocated to the non-septic SIRS, sepsis or septic shock groups according to microbiological results because knowledge of previously measured procalcitonin concentration may affect group-allocation. Plasma PCT was measured by immunoluminometric assay (LUMI test PCT, Brahms Diagnostica, Berlin, Germany) and plasma CRP was measured by latex turbidimetric immunoassay.

Sepsis-related organ failure assessment score (SOFA score)[10] was calculated at the time of measurements of plasma PCT and CRP to evaluate the relationship between plasma PCT or CRP level and SOFA score. The SOFA score was calculated using the total scores for 6 organs (lung, coagulation system, liver, heart and vessel, central nervous system and kidney) with scores ranging from 0 (normal) to 4 (most abnormal) for each organ to describe quantitatively and as objectively as possible the degree of organ failure over time; however, neurological evaluation was not performed because of frequent use of sedative agents in the critically ill patients (hence, in this study the maximum score was 20).

In 4 patients without any complications before minor surgery, plasma PCT and CRP levels were measured as a control group.

Values are shown as median (minimum, maximum). Comparisons between groups were performed by the Mann-Whitney U test and Kruskal-Wallis non-parametric analysis of variance. Relationships between SOFA score and PCT or CRP were examined by analysis of linear regression with the use of the least-squares method and Spearman's rank correlation coefficient. *P* values less than 0.05 were considered significant.

Results

Demographic data for the patients of each group are listed in Table I.

TABLE I: DEMOGRAPHIC DATA FOR PATIENTS FOR EACH GROUP

	Non-septic SIRS	Sepsis	Septic Shock
No.	16	7	12
Median age (y) (minimum, maximum)	55 (17, 71)	48 (25, 75)	63 (25, 73)
Male/Female	10/6	6/1	6/6
Mortality	2 (13%)	4 (57%)	5 (42%)

SIRS: systemic inflammatory response syndrome

In all 4 patients in the control group, plasma PCT levels were <0.12 ng/mL and plasma CRP levels were <0.1 mg/dL.

The median (minimum, maximum) plasma PCT and CRP levels and SOFA score on the day when patients were diagnosed with non-septic SIRS, sepsis or septic shock were 0.6 (0.1, 3.4) ng/mL, 13.8 (0.3, 48.8) mg/dL and 4 (0, 9) in the non-septic SIRS group; 5.4 (0.9, 47.7) ng/mL, 23.3 (1.4, 26.6) mg/dL and 10 (1, 13) in the sepsis group; and 73.4 (9.6, 824.1) ng/mL, 17.4 (2.2, 34.1) mg/dL and 12 (5, 16) in the septic shock group (Table II). Significant differences among the three groups existed in plasma PCT levels but not in plasma CRP levels (Fig.1). SOFA scores in the sepsis and septic shock groups were significantly higher than that in the non-septic SIRS group (Table II).

A good correlation was found between plasma PCT level and SOFA score ($r_s = 0.766$, $P < 0.0001$) (Fig. 2), although no correlation was found between CRP level and SOFA score (Fig. 3).

Discussion

It is known that levels of cytokines such as tumour necrosis factor-α and interleukin-6 are rapidly increased with the onset of severe infection and that these cytokine levels are of prognostic value in predicting the severity and outcome of sepsis.[11,12] However, direct measurements of

TABLE II: MEDIAN (MINIMUM, MAXIMUM) PLASMA PROCALCITONIN AND CRP LEVELS AND SOFA SCORE FOR EACH GROUP ON THE DAY OF DIAGNOSIS OF PATIENTS WITH NON-SEPTIC SIRS, SEPSIS OR SEPTIC SHOCK

	Non-septic SIRS	Sepsis	Septic shock
Procalcitonin (ng/mL)	0.6 (0.1, 3.4)	5.4 (0.9, 47.7)	73.4 (9.6, 824.1)
CRP (mg/dL)	13.8 (0.3, 48.8)	23.3 (1.4, 26.6)	17.4 (2.2, 34.1)
SOFA score	4 (0, 9)	10 (1, 13)	12 (5, 16)

CRP: C-reactive protein; SIRS: systemic inflammatory response syndrome; SOFA: sepsis-related organ failure assessment

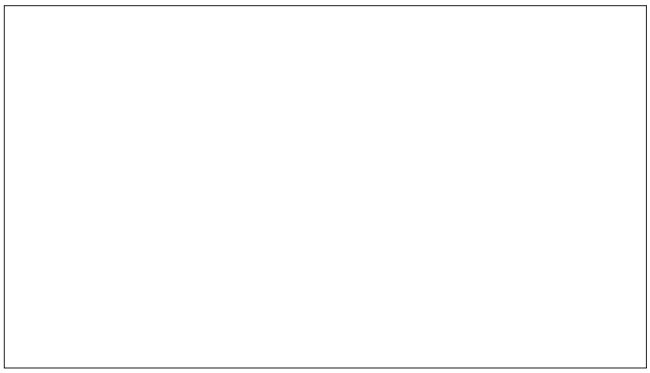

Fig. 1. Plasma procalcitonin and C-reactive protein (CRP) levels on the day of diagnosis of patients with non- septic systemic inflammatory response syndrome (SIRS), sepsis or septic shock.

Fig. 2. Correlation between plasma procalcitonin level and Sepsis-related Organ Failure Assessment (SOFA) score (r_s = 0.766, P <0.0001). Solid lines link the first and second measurements for the same patient.

these cytokines in the clinical setting are not feasible at present since the results of such measurements are not quickly available. Investigation of surrogate markers for cytokines is thus useful. Among the 4 surrogate markers (leukocyte count, body temperature, CRP or PCT), leukocyte count and body temperature are markers of both infectious and non-infectious systemic inflammation and thus unreliable for diagnosis of infection.

It has been reported that daily measurement of CRP is useful in the detection of sepsis and is more sensitive in this respect than body temperature and leukocyte count.[1] However, CRP level may increase following severe non-septic SIRS. In the present study, CRP level increased markedly in all groups i.e., the non-septic SIRS, sepsis and septic shock groups, and no significant differences existed

Fig. 3. Correlation between plasma C-reactive protein (CRP) level and Sepsis-related Organ Failure Assessment (SOFA) score. Solid lines link the first and second measurements for the same patient.

in CRP levels among these three groups. CRP may thus not be a good indicator of infection in patients with severe SIRS.

The half-life of PCT is 22 to 29 hours, and this value is not significantly altered by renal dysfunction.[13] Because of its long half-life, PCT is detectable when screened for on a daily basis.[12] PCT can also serve as an early (within 6 hours) marker of infection and inflammation.[12] Measurement of PCT with immunoluminometric assay (LUMI test PCT) is easy and can be completed within 2 hours, and is therefore feasible and useful in the clinical setting.

In the present study, PCT increased slightly in the patients with non-septic SIRS but markedly in the patients with sepsis or septic shock, with significant differences among the three groups. PCT level can differentiate between presence or absence of infection in patients with severe SIRS, and PCT is a good indicator of severity of sepsis. It has recently been reported that PCT is useful as an early marker for discriminating between sepsis and severe sepsis.[14]

In the present study, we did not attempt to determine cut-off values for sepsis because we have few patients and measurements of procalcitonin; though in a previous burn study,[15] a cut-off value of 3 ng/mL of procalcitonin was taken to indicate sepsis.

In the present study, a good correlation was found between PCT level and SOFA score, although no correlation was found between CRP level and SOFA score. Meisner et

al[16] also reported that SOFA score increased as PCT increased. PCT thus appears to be a good indicator of severity of organ failure in patients with sepsis.

It has been demonstrated in experimental sepsis[17] that increased procalcitonin increases mortality, whereas neutralisation of procalcitonin increases survival. Although the role of procalcitonin in the process of sepsis in humans is unclear, procalcitonin might be of considerable functional importance.

In conclusion, plasma PCT level is useful for the diagnosis of sepsis in patients with severe SIRS and as an indicator of severity of sepsis in such patients.

REFERENCES

1. Póvoa P, Almeida E, Moreira P, Fernandes A, Mealha R, Aragão A, et al. C-reactive protein as an indicator of sepsis. Intensive Care Med 1998; 24:1052-6.
2. Adamik B, Kübler-Kielb J, Golebiowoska B, Gamian A, Kübler A. Effect of sepsis and cardiac surgery with cardiopulmonary bypass on plasma level of nitric oxide metabolites, neopterin, and procalcitonin: correlation with mortality and postoperative complications. Intensive Care Med 2000; 26:1259-67.
3. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993; 341:515-8.
4. Russwurm S, Wiederhold M, Oberhoffer M, Stonans I, Zipfel PF, Reinhart K. Molecular aspects and natural source of procalcitonin. Clin Chem Lab Med 1999; 37:789-97.
5. Nijsten M W N, Olinga P, The T H, de Vries E G E, Koops H S, Groothuis G M M, et al. Procalcitonin behaves as a fast responding acute phase protein *in vivo* and *in vitro*. Crit Care Med 2000; 28:458-61.
6. Ugarte H, Silva E, Mercan D, Mendonça A D, Vincent J-L. Procalcitonin used as a marker of infection in the intensive care unit. Crit Care Med 1999; 27:498-504.
7. Müller B, Becker K L, Schächinger H, Rickenbacher P R, Huber P R, Zimmerli W, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med 2000; 28:977-83.
8. Gendrel D, Raymond J, Coste J, Moulin F, Lorrot M, Guérin S, et al. Comparison of procalcitonin with C-reactive protein, interleukin6 and interferon-alpha for differentiation of bacterial vs. viral infections. Pediatr Infect Dis J 1999; 18:875-81.
9. American College of Chest Physicians/Society of Critical Care Medicine consensus conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20:864-74.
10. Vincent J-L, Moreno R, Takala J, Willatts S, DeMendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22: 707-10.
11. Dandona P, Nix D, Wilson M F, Aljada A, Love J, Assicot M, et al. Procalcitonin increase after endotoxin injection in normal subject. J Clin Endocrinol Metab 1994; 79:1605-8.
12. Oberhoffer M, Karzai W, Meier-Hellmann A, Bögel D, Fassbinder J, Reinhart K. Sensitivity and specificity of various markers of inflammation for the prediction of tumor necrosis factor-α and interleukin-6 in patients with sepsis. Crit Care Med 1999; 27:1814-8.
13. Meisner M, Schmidt J, Hüttner H, Tschaikowsky K. The natural elimination rate of procalcitonin in patients with normal and impaired renal function. Intensive Care Med 2000; 26:S212-6.
14. Brunkhorst F M, Wegscheider K, Forycki Z F, Brunkhorst R. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. Intensive Care Med 2000; 26:S148-52.
15. von Heimburg D, Stieghorst W, Khorram-Sefat R, Pallua N. Procalcitonin —a sepsis parameter in severe burn injuries. Burns 1998; 24:745-50.
16. Meisner M, Tschaikowsky K, Palmaers T, Schmidt J. Comparison of procalcitonin (PCT) and C-reactive protein (CRP) plasma concentrations at different SOFA scores during the course of sepsis and MODS. Crit Care (Lond) 1999; 3:45-55.
17. Nylen E S, Whang K T, Snider R H, Steinwald P M, White J C, Becker K L. Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. Crit Care Med 1998; 26:1001-6.