Original Article

http://dx.doi.org/10.3349/ymj.2014.55.4.975
pISSN: 0513-5796, eISSN: 1976-2437

Yonsei Med J 55(4):975-979, 2014

YMJ

Usefulness of the Endotoxin Activity Assay to Evaluate the Degree of Lung Injury

Yuichiro Sakamoto, Satoshi Inoue, Takashi Iwamura, Tomoko Yamashita, Atsushi Nakashima, Hiroyuki Koami, Toru Miike, Mayuko Yahata, Hisashi Imahase, Akiko Goto, Showgo Narumi, Miho Ohta, and Chris-Kosuke Yamada

Department of Emergency and Critical Care Medicine, Faculty of Medicine, Saga University, Saga, Japan.

Received: April 9, 2013
Revised: August 30, 2013
Accepted: October 10, 2013
Corresponding author: Dr. Yuichiro Sakamoto, Department of Emergency and Critical Care Medicine, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan.
Tel: 81-952-34-3160, Fax: 81-952-34-1061
E-mail: sakamoy@cc.saga-u.ac.jp

· The authors have no financial conflicts of interest.

Purpose: It has been reported that the Pulse Contour Cardiac Output (PiCCO) is very useful mainly in the field of intensive care and treatment to grasp the pathophysiological conditions of pulmonary edema because of its capability of obtaining data such as Pulmonary Vascular Permeability Index (PVPI) and Extra Vascular Lung Water (EVLW). Furthermore, a high degree of usability of various markers has been reported for better understanding of the pathological conditions in cases with septicemia. **Materials and Methods:** The correlation between the cardiorespiratory status based upon the PiCCO monitor (EVLW and PVPI) and inflammatory markers including C reactive protein, procalcitonin (PC), and Endotoxin Activity Assay (EAA) were evaluated in 11 severe cases that required treatment with a respirator in an intensive care unit. **Results:** The EAA values were significantly higher in patients with abnormal EVLW at 0.46±0.20 compared to the normal EVLW group at 0.21±0.19 (p=0.0064). In a similar fashion, patients with abnormal PVPI values tended to have higher PC levels at 18.9±21.8 compared to normal PVPI cases at 2.4±2.2 (p=0.0676). On the other hand, PVPI was significantly higher in the abnormal EAA group at 3.55±0.48 in comparison with the normal EAA group at 1.99±0.68 (p=0.0029). The abnormal EAA group tended to have higher PVPI values than the normal EAA group. **Conclusion:** The EAA is a measurement method designed to estimate the activity of endotoxins in the whole blood. Our results suggest that the EAA value, which had the greatest correlation with lung disorders diagnosed by the PiCCO monitoring, reflects inflammatory reactions predominantly in the lungs.

Key Words: Pulse Contour Cardiac Output (PiCCO), CRP, procalcitonin, Endotoxin Activity Assay (EAA)

INTRODUCTION

The Pulse Contour Cardiac Output (PiCCO) has become to be widely used in Japan in recent years. It has been reported that the PiCCO is very useful mainly in the field of intensive care and treatment to evaluate pathophysiological conditions

of pulmonary edema because of its ability to obtain data such as Extra Vascular Lung Water (EVLW) and Pulmonary Vascular Permeability Index (PVPI).[1] A high degree of usability of various inflammatory markers has been reported for better understanding of the pathological conditions in cases with septicemia that require an intensive care. White blood cell count and C reactive protein (CRP) have been the most commonly used markers to evaluate an inflammatory response of patients in Japan. The CRP is widely known to be an acute inflammatory maker and is well correlated with respiratory tract infections.[2] The procalcitonin (PC) is also reported to relate closely to the severity of respiratory tract infections and is incorporated in the administration protocol for antimicrobial agent selection.[3,4] The inflammatory cytokines reflect the degree of inflammatory reaction more sensitively. However, since very few institutions are equipped with the facility capable of rapid measurement of cytokines, it is not widely applied in a clinical setting. On the other hand, there are some versatile ways to assess the status of septicemia in patients such as qualitative PC kit and Endotoxin Activity Assay (EAA)[5,6] by which result can be obtained within 10 or 20 minutes. The higher EAA levels are correlated with a higher risk of mortality, as well as an increased risk for developing sepsis. Therefore, it is expected that these ways of measurement will be more incorporated into clinics when doctors make decisions for treatment strategies for patients with sepsis.

Table 1. Patient Characteristics

Characteristics	Data
No. of patients	11
Sex (male/female)	8/3
Age (yrs), mean±SE	62.6±19.1
PiCCO data	
EVLW	14.5±5.6
PVPI	2.6±1.0

PiCCO, Pulse Contour Cardiac Output; EVLW, Extra Vascular Lung Water; PVPI, Pulmonary Vascular Permeability Index.

Table 2. Underlying Diseases (n=11)

Underlying diseases	Data
Trauma	6 cases
Post resuscitation encephalosis	2 cases
Peritonitis	1 case
Retroperitoneal abscess	1 case
AAA rupture	1 case

AAA, abdominal aortic aneurysm.

MATERIALS AND METHODS

We evaluated the correlation between the cardiorespiratory status based upon the PiCCO monitor and inflammatory markers including CRP, PC, and EAA in 11 severe cases that required treatment with a respirator in an intensive care unit (ICU). Particularly, patients were divided into either the normal EVLW group (EVLW-N: EVLW<9.0) or the abnormal EVLW group (EVLW-A: EVLW>9.1) and correlation with inflammatory markers including EAA, PC, and CRP were evaluated. Likewise, patients were divided into either the normal PVPI group (PVPI-N: PVPI<3.0) or the abnormal PVPI group (PVPI-N: PVPI>3.1) and correlation with inflammatory markers were evaluated. Furthermore, the EAA, PC, and CRP were also divided into either normal (EAA-N, PC-N, and CRP-N) or abnormal (EAA-A, PC-A, and CRP-A) groups and correlation with EVLW and PVPI were verified vise versa. The high cutoff values of each inflammatory marker were set at greater than 0.5, 0.5, and 10 respectively, because these cutoff values are expected to be high enough to reflect the presence of infectious diseases.

RESULTS

The average age of patients included in this study was 62.6±19.1, with eight males and three females (Table 1). All patients in this study were severe cases which required treatment in the ICU. Underlying diseases were: six trauma cases, two cases of postresuscitation encephalopathy, one peritonitis, one retroperitoneal abscess, and one case with ruptured abdominal aortic aneurysm (Table 2). The EAA values were significantly higher in the EVLW-A at 0.46±0.20 compared to the EVLW-N at 0.21±0.19 (p=0.0064) and no correlations between EVLW and PC or CRP were observed (Fig. 1). In a similar fashion, PVPI-A tended to have higher PC levels at 18.9±21.8 compared to PVPI-N at 2.4±2.2 (p=0.0676), however, no correlations between PVPI level and EAA or CRP were observed (Fig. 2).

On the other hand, the value of PVPI was significantly higher in the EAA-A at 3.55±0.48 in comparison with EAA-N at 1.99±0.68 (p=0.0029). There was a tendency that EAA-A had higher PVPI values than EAA-N (Fig. 3). The CRP did not have any statistical significance with either EVLW or PVPI (data not shown). Neither EVLW nor PVPI showed any correlation with PC values (Fig. 4).

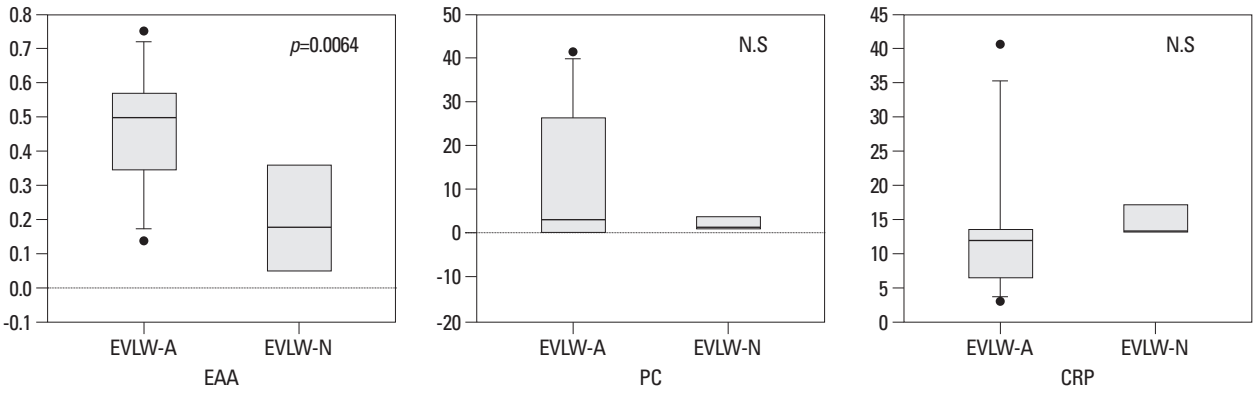

Fig. 1. Relationship between EVLW and inflammatory marker. The EAA values were significantly higher in the EVLW-A at 0.46±0.20 compared to the EVLW-N at 0.21±0.19 (p=0.0064) and no correlations between EVLW and PC or CRP were observed. EAA, Endotoxin Activity Assay; PC, procalcitonin; CRP, C reactive protein; EVLW, Extra Vascular Lung Water.

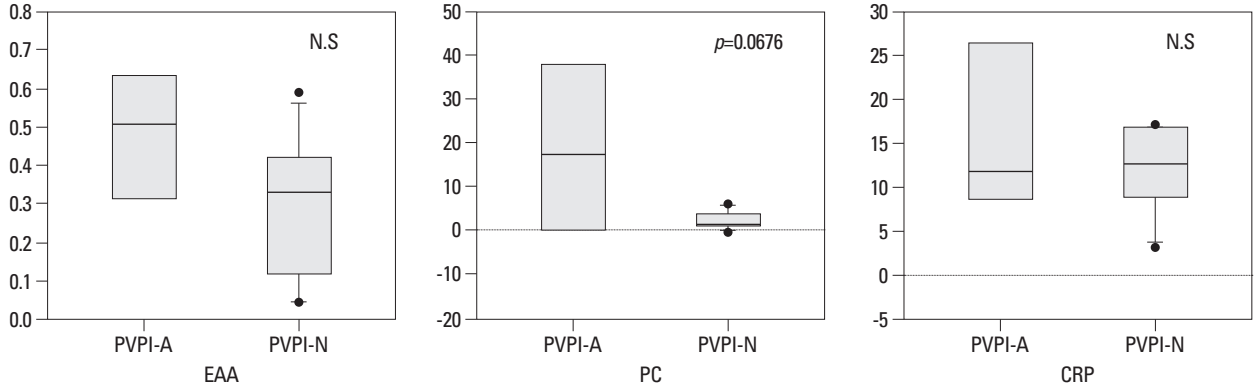

Fig. 2. Relationship between PVPI and inflammatory marker. The PVPI-A tended to have higher PC levels at 18.9±21.8 compared to PVPI-N at 2.4±2.2 (p=0.0676), and no correlations between PVPI level and EAA or CRP were observed. EAA, Endotoxin Activity Assay; PC, procalcitonin; CRP, C reactive protein; PVPI, Pulmonary Vascular Permeability Index.

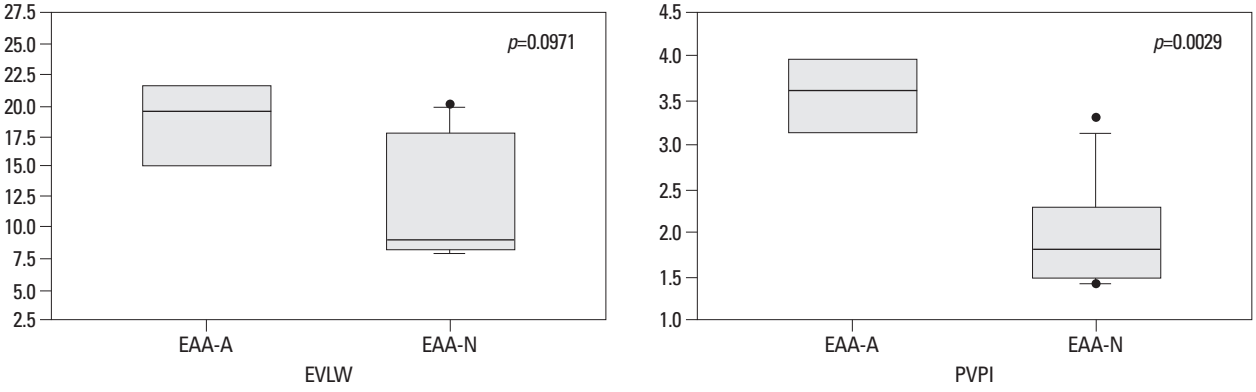

Fig. 3. Relationship between EAA and PiCCO data. The PVPI values were significantly higher in the EAA-A at 3.55±0.48 in comparison with EAA-N at 1.99±0.68 (p=0.0029). There was a tendency that EAA-A has higher PVPI values than EAA-N. EAA, Endotoxin Activity Assay; PiCCO, Pulse Contour Cardiac Output; PVPI, Pulmonary Vascular Permeability Index.

Statistical analysis

The approval of our institution's ethics committee and informed consent were obtained. The results were expressed as the mean±SD. Differences were analyzed using the Wilcoxon generalized test. A p-value less than 0.05 was regarded as statistically significant.

DISCUSSION

The Swan-Ganz catheter has been used to monitor cardiac functions and circulatory dynamics of the patients with septic shock requiring intensive care and treatment for a long

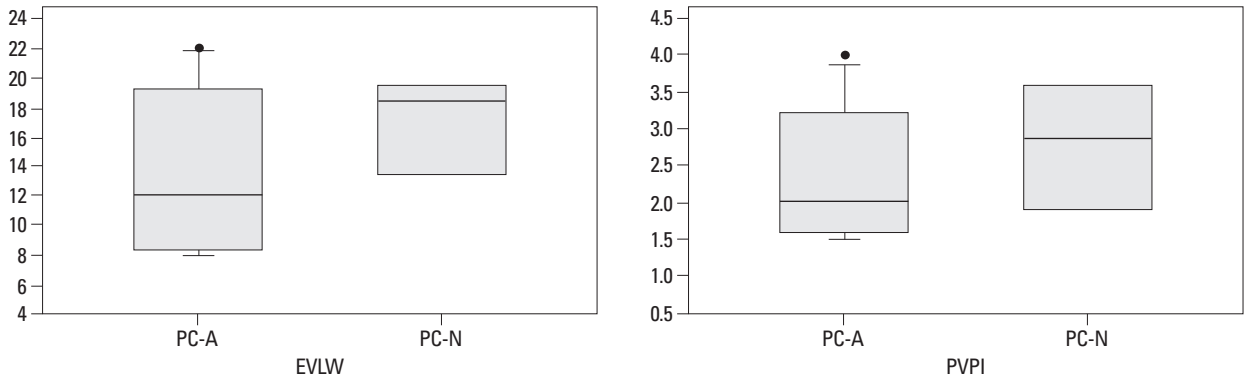

Fig. 4. Relationship between PC and PiCCO data. The PC values didn't significantly correlate with either EVLW or PVPI. PC, procalcitonin; PiCCO, Pulse Contour Cardiac Output; PVPI, Pulmonary Vascular Permeability Index; EVLW, Extra Vascular Lung Water.

time. In recent years, the benefits of using the PiCCO monitor which can calculate extra vascular lung water and the pulmonary vascular permeability index to comprehend more detailed pathological conditions of the patients with sepsis has been reported in Japan and other countries.[1,7,8]

The utilities of inflammatory markers measured by blood tests have also reported to be effective when doctors decide treatment strategies for septic patients. Especially in European countries, the usefulness of PC to evaluate the severity of septicemia is largely known.[9] Although its test results represent patients' inflammatory reactions 20 hours before, the CRP, whose result can be obtained rapidly, is widely used as an inflammatory maker. However, the CRP is said to increase even in patients with severe external injuries without any evidence of infections so that it is unsuitable for the diagnosis of infectious diseases.[10] Since high inflammatory blood cytokines play a main role in the pathological conditions of septicemia, it is believed that measuring inflammatory cytokines such as interleukin-6 (IL-6) is the most reliable method to interpret the pathological conditions of sepsis.[11,12] However, currently very few hospitals institutions are able to obtain cytokine level rapidly. Therefore, an invention and commercialization of simple kits that can rapidly measure cytokines such as IL-6, TNF-α, and IL-1 are anticipated.

The usefulness of EAA, which is designed to represent the activity of endotoxins in the blood to grasp pathophysiological conditions of septic patients, has been reported. However, since the EAA represents the activity of endotoxins indirectly through a measurement of the neutrophil activation, it is still controversial whether or not the EAA actually reflects the endotoxin levels. Despite its disadvantage in direct evaluation of the endotoxin status, the EAA is capable of getting results rapidly at the bedside of patients and is highly expected to be a useful inflammatory marker. The present data shows that the group with possible lung injury based upon high level of EVLW or PVPI had abnormal level of inflammatory markers. Unfortunately, relationships between EVLW and EAA were not consistent. Namely, the EVLW-A group had a significantly higher EAA level, whereas the EAA-A group did not show a significantly higher EVLW level. One of the possible reasons for this would be a huge difference in normal value range between EVLW and EAA. The usefulness of the EAA has been reported mainly in other clinical trials.[13,14] On the whole, our results suggested that the EAA values, which was correlated the most with lung injury according to the PiCCO monitoring, reflect inflammatory reactions in the lungs.

REFERENCES

1. Ritter S, Rudiger A, Maggiorini M. Transpulmonary thermodilution-derived cardiac function index identifies cardiac dysfunction in acute heart failure and septic patients: an observational study. Crit Care 2009;13:R133.
2. Smith RP, Lipworth BJ. C-reactive protein in simple community-acquired pneumonia. Chest 1995;107:1028-31.
3. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 2009;302:1059-66.
4. Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. Arch Intern Med 2008;168:2000-7.
5. Marshall JC, Walker PM, Foster DM, Harris D, Ribeiro M, Paice J, et al. Measurement of endotoxin activity in critically ill patients using whole blood neutrophil dependent chemiluminescence. Crit Care 2002;6:342-8.
6. Marshall JC, Foster D, Vincent JL, Cook DJ, Cohen J, Dellinger RP, et al. Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study. J Infect Dis 2004;

190:527-34.
7. Pino-Sánchez F, Lara-Rosales R, Guerrero-López F, Chamorro-Marín V, Navarrete-Navarro P, Carazo-de la Fuente E, et al. Influence of extravascular lung water determination in fluid and vasoactive therapy. J Trauma 2009;67:1220-4.
8. Uchino S, Bellomo R, Morimatsu H, Sugihara M, French C, Stephens D, et al. Pulmonary artery catheter versus pulse contour analysis: a prospective epidemiological study. Crit Care 2006;10:R174.
9. 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.
10. Endo S, Aikawa N, Fujishima S, Sekine I, Kogawa K, Yamamoto Y, et al. Usefulness of procalcitonin serum level for the discrimination of severe sepsis from sepsis: a multicenter prospective study. J Infect Chemother 2008;14:244-9.
11. Bozza FA, Salluh JI, Japiassu AM, Soares M, Assis EF, Gomes RN, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. Crit Care 2007;11:R49.
12. Nakada TA, Hirasawa H, Oda S, Shiga H, Matsuda K. Blood purification for hypercytokinemia. Transfus Apher Sci 2006;35:253-64.
13. Romaschin AD, Harris DM, Ribeiro MB, Paice J, Foster DM, Walker PM, et al. A rapid assay of endotoxin in whole blood using autologous neutrophil dependent chemiluminescence. J Immunol Methods 1998;212:169-85.
14. Monti G, Bottiroli M, Pizzilli G, Minnini M, Terzi V, Vecchi I, et al. Endotoxin activity level and septic shock: a possible role for specific anti-endotoxin therapy? Contrib Nephrol 2010;167:102-10.