Predictive Value of Procalcitonin for Infection and Survival in Adult Cardiogenic Shock Patients Treated with Extracorporeal Membrane Oxygenation

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Procalcitonin (PCT) is a predictive marker for the occurrence of bacterial infection and the decision to terminate antibiotic treatment in critically ill patients. An unusual increase in PCT, regardless of infection, has been observed during extracorporeal membrane oxygenation (ECMO) support. We evaluated trends and the predictive value of PCT levels in adult cardiogenic shock during treatment with ECMO. We reviewed the clinical records of 38 adult cardiogenic shock patients undergoing veno-arterial ECMO support between January 2014 and December 2016. The exclusion criteria were age < 18 years, pre-ECMO infection, and less than 48 hours of support. The mean patient age was 56.7±14.7 years and 12 (31.6%) patients were female. The mean duration of ECMO support was 9.0±7.6 days. The rates of successful ECMO weaning and survival to discharge were 55.3% (n=21) and 52.6% (n=20), respectively. There were 17 nosocomial infections in 16 (42.1%) patients. Peak PCT levels (mean 25.6±9.4 ng/mL) were reached within 48 hours after initiation of ECMO support and decreased to ≤5 ng/mL within one week. The change in PCT levels was not useful in predicting the occurrence of new nosocomial infections during the ECMO run. However, a PCT level > 10 ng/mL during the first week of ECMO support was significantly associated with mortality (p < 0.01). The change in PCT level was not useful in predicting new infection during ECMO support. However, higher PCT levels within the first week of the ECMO run are associated with significantly higher mortality.

Key Words: Extracorporeal membrane oxygenation; Calcitonin; Cross infection; Shock; Cardiogenic

INTRODUCTION

The clinical outcomes of extracorporeal membrane oxygenation (ECMO) show ongoing improvement, and ECMO treatment currently focuses on the control of complications.[1] Nosocomial infections are among the major complications that increase patient mortality during ECMO.[2] Unfortunately, the use of extracorporeal circulation itself may be a cause of systemic inflammatory response syndrome (SIRS). Therefore, it may be difficult to differentiate between infectious complications arising early after ECMO is initiated and the general inflammatory response to the use of extracorporeal circulation.

Various methods for the diagnosis of infection have been studied. Biomarkers such as white blood cells (WBCs) and C-reactive protein (CRP), in addition to blood cultures, have been used in diagnosis. Existing biomarkers in patients with suspected infection have limitations in sensitivity and specificity, and blood cultures are slow to identify organisms, with the possibility of false negatives. Procalcitonin (PCT) is the peptide precursor of the hormone calcitonin, and under normal circumstances is produced in the thyroid parafollicular cell (normal serum concentration < 0.05 ng/mL). The PCT level has proven to be highly spe-

cific, and is a predictive marker for occurrence of bacterial infection and the decision to terminate antibiotic treatment in critically ill patients.[3,4]

However, in addition to infectious disease, PCT is also elevated in a variety of illnesses that cause inflammatory reactions such as complications associated with abdominal surgery, transplantation, trauma, and burns.[3-5] Recently, its usefulness has been confirmed in non-infectious diseases such as ischemic stroke.[6] An unusual increase in PCT, regardless of infection, has also been observed during ECMO support.[7,8] We evaluated trends and predictive value of PCT levels measured during ECMO for prediction of clinical outcomes, such as infection and survival.

MATERIALS AND METHODS

1. Patient selection

This retrospective study included consecutive adult cardiogenic shock patients undergoing veno-arterial (VA)-ECMO support between January 2014 and December 2016 at the Department of Thoracic and Cardiovascular Surgery, Chonnam National University Hospital (CNUH). The exclusion criteria were use of extracorporeal cardiopulmonary resuscitation, age ≤18 years, use of veno-venous or veno-arterial venous ECMO, and inadequate data about PCT levels. Patients who underwent ECMO for less than 48 hours were not included, since they were not exposed long enough to identify ECMO-related infection events (Fig. 1).

2. ECMO protocol

The basic principles of the ECMO procedure and patient care were described in a previous study.[9] Briefly, ECMO cannulation was performed in a sterile fashion with chlorhexidine painting. A permanent life support system with a polymethylpentene-type oxygenator (Maquet Inc., Hirrlingen, Germany) was applied. Heparin was used as an anticoagulant. the cannulation mode, size, and approach site were determined by the surgeon according to
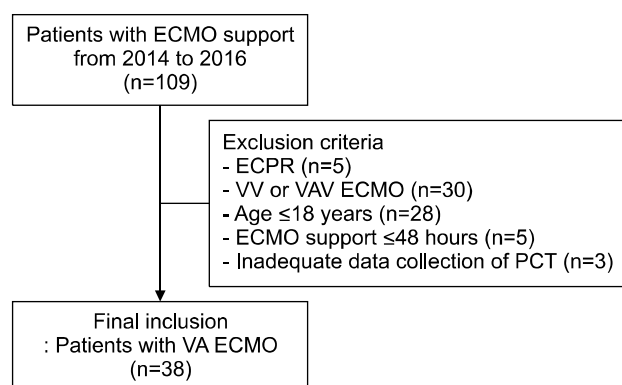
body weight, height, and vessel size. A peripheral approach using the femoral artery and vein was the predominant method used in the study. If there was no specific culture or clinical evidence of ongoing infection, we did not routinely use prophylactic antibiotics with either open or percutaneous cannulation. In general, the management protocol for ECMO followed the Extracorporeal Life Support Organization guidelines.[10]

3. Data collection

Baseline characteristics and operative information including age, sex, underlying conditions, pre-ECMO laboratory findings, duration of hospital and intensive care unit (ICU) stay before ECMO, shock to ECMO time, and duration of ECMO support were collected and evaluated. Weaning success after ECMO support, survival to discharge, and infection incidence on ECMO were assessed using hospital records. When possible, routine daily quantitative PCT measurement (VIDAS BRAHMS PCT; Biomerieux, France) was performed in the CNUH labo-

TABLE 1. Patients' characteristics before ECMO support

	Variable[a]
Number of patients	38
Age (year)	56.7±14.7
Male	26 (68.4)
Body weight (kg)	63.7±9.5
Underlying disease	
CAD	4 (10.5)
DM	14 (36.8)
HTN	14 (36.8)
COPD	2 (5.3)
AKI	6 (15.8)
Laboratory findings	
White blood cell (10^3/mm^3)	13.9±5.4
Hemoglobin, g/dL	12.1±2.5
Platelets (10^3/mm^3)	207.6±59.8
Total bilirubin (mg/dL)	1.10±1.0
Creatinine (mg/dL)	1.2±0.8
CRP (mg/dL)	3.9±4.2
Clinical conditions	
Pre-ECMO hospital stay (day)	3.6±8.9
Pre-ECMO ICU stay (day)	0.9±0.5
Shock to ECMO time (hour)	5.3±9.0
Causes of ECMO support	
CAD	17 (44.7)
AFM	10 (26.3)
CPB weaning failure	8 (21.1)
Sepsis	3 (7.9)

AFM: acute fulminant myocarditis, ECMO: extracorporeal membrane oxygenation, CAD: coronary artery disease, CPB: cardiopulmonary bypass, DM: diabetus mellitus, HTN: hypertension, COPD: chronic obstructive lung disease, AKI: acute kidney injury, CRP: C-reactive protein, ICU: intensive care unit.
[a]Data are presented as the number of cases (%) for categorical variables or as means±standard deviations for continuous variables.

FIG. 1. Algorithm of patient selection in our study. ECMO: extracorporeal membrane oxygenation, ECPR: extracorporeal cardiopulmonary resuscitation, VA: veno-arterial, VAV: veno-arterial venous, VV: veno-venous, PCT: procalcitonin.

ratory during ECMO support.

Nosocomial infection during ECMO support was defined according to the criteria of the Centers for Disease Control and Prevention, as follows: a case with confirmed organisms from one or more blood, respiratory, or urinary culture during the period 48 hours after the initiation of ECMO to 24 hours after ECMO weaning.[11] Microbiological isolations were correlated with clinical symptoms and typical inflammatory characteristics in blood samples and radiographic findings. The primary outcome was in-hospital mortality and the secondary outcome was new-onset nosocomial infection.

TABLE 2. Early outomes of ECMO support

	Variable[a]
Number of patients	38
Duration of ECMO support (day)	9.0±7.6
ECMO support >7 days	24 (63.2)
ECMO weaning	21 (55.3)
Survival to discharge	20 (52.6)
Nosocomial infection during ECMO support	16 (42.1)

ECMO: extracorporeal membrane oxygenation. [a]Data are presented as the number of cases (%) for categorical variables or as means±standard deviations for continuous variables.

4. Statistical analysis

Data are presented as the number of cases (percentage) for categorical variables or as mean values with standard deviations for continuous variables. The Mann-Whitney test and chi-square test were used to compare the risk factors related to occurrence of survival and nosocomial infection. We performed logistic regression using survival as the dependent variable. All variables with $p < 0.05$ in univariate analyses were included in the multivariate regression model. Differences between groups in mean PCT values within the first week according to survival were compared using repeated measures analysis of variance. Survival probability was calculated using the Kaplan-Meier survival analysis. Statistical analysis was performed using the MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017). In all analyses, p-values < 0.05 were considered statistically significant.

5. Ethics statement

This study was approved by the Institutional Review Board of CNUH, which waived the requirement for informed patient consent based on the retrospective nature

TABLE 3. Univariate analysis of risk factors for nosocomial infection before and during ECMO support

	No Infection[a] (n=22)	Infection[a] (n=16)	p-value
Age	61.5±11.3	64.8±9.7	0.39
Male	16 (72.7)	10 (62.5)	0.54
Body weight (kg)	64.3±6.6	63.0±12.8	0.69
Underlying disease			
CAD	2 (9.1)	2 (12.5)	0.74
DM	4 (18.2)	6 (37.5)	0.15
HTN	4 (18.2)	6 (37.5)	0.15
COPD	0	2 (12.5)	0.09
AKI	4 (18.2)	2 (12.5)	0.64
Laboratory findings before ECMO support			
White blood cell (10^3/mm^3)	14.0±6.3	13.8±4.6	0.91
Hemoglobin, g/dL	13.2±2.2	12.7±2.8	0.24
Platelets (10^3/mm^3)	201.5±66.1	216.0±51.0	0.47
Total bilirubin (mg/dL)	1.5±1.3	1.3±0.9	0.83
Creatinine (mg/dL)	1.0±0.4	1.1±1.1	0.51
CRP (mg/dL)	3.4±2.5	4.5±5.6	0.44
Clinical conditions before ECMO support			
Pre-ECMO hospital stay (day)	4.3±11.6	2.7±3.3	0.61
Pre-ECMO ICU stay (day)	0.9±0.3	1.0±0.7	0.6
Shock to ECMO time (hour)	7.2±11.5	2.9±2.3	0.15
Clinical outomes during ECMO support			
Duration of ECMO support (day)	5.4±1.4	14.0±9.8	<0.01
ECMO time >7 days	2 (9.1)	12 (75)	<0.01
Peak value of PCT within first week (pg/dL)	31.3±38.9	50.5±42.4	0.16
Peak value of PCT >10 (pg/dL) within first week	10 (45.5)	12 (75)	0.67

ECMO: extracorporeal membrane oxygenation, CAD: coronary artery disease, DM: diabetus mellitus, HTN: hypertension, COPD: chronic obstructive lung disease, AKI: acute kidney injury, CRP: C-reactive protein, ICU: intensive care, PCT: procalcitonin. [a]Data are presented as the number of cases (%) for categorical variables or as means±standard deviations for continuous variables.

of the work (IRB No: CNUH-2017-314).

RESULTS

1. Patient Demographics and early outcomes of ECMO support

The mean patient age at the time of ECMO support was 56.7±14.7 years and 26 (68.4) patients were male. Among these, 14 (36.8%) patients had hypertension. Hospital and ICU stays before ECMO were 3.6±8.9 and 0.9±0.5 days, respectively. The duration of shock before ECMO initiation was 5.3±9.0 hours. Patient characteristics before ECMO support are summarized in Table 1. VA ECMO was the predominant type used in 92.1% (n=35) of patients. Veno-veno-arterial ECMO was used in 3 patients (7.9%). The duration of ECMO support was 9.0±7.6 days. Twenty-four (63.2%) patients received ECMO support for more than 7 days. There were 17 nosocomial infections in 16 (42.1%) patients. The rates of weaning success and survival to discharge were 55.3% (n=21) and 52.6% (n=20), respectively. The early outcomes of ECMO support are summarized in Table 2.

2. Statistical analysis of risk factors for survival

The baseline characteristics of 16 patients with infection

and 22 without infection are shown in Table 3. There were no significant differences between the 2 groups in terms of sex, body weight, underlying disease, laboratory findings before ECMO support, ICU and hospital stay before ECMO, and shock to ECMO time. The duration of ECMO support was the only risk factor for occurrence of nosocomial infection during ECMO (p < 0.01). However, the increase in PCT levels within the first week was not useful in predicting the occurrence of a new nosocomial infection during the ECMO run. The results of risk factor analysis for survival before and during ECMO support are summarized in Table 4. There were no significant differences between the 2 groups in terms of sex, body weight, underlying disease, laboratory findings before ECMO support, duration of ICU and hospital stay before ECMO, shock to ECMO time, and duration of ECMO support. The survivor group was younger than the non-survivor group (p=0.03). The non-survivor group had a higher incidence of nosocomial infection (p < 0.01) and higher peak PCT levels (p < 0.01). In logistic regression analysis, an independent predictor of survival before and during ECMO support was a higher peak PCT value (adjusted odds ratio, 1.94; 95% confidence interval, 1.03-3.27; p=0.01) (Table 5).

TABLE 4. Univariate analysis of risk factors for survival before and during ECMO support

	Survivor[a] (n=20)	Non-survivor[a] (n=18)	p-value
Age (year)	51.9±13.9	62.2±14.2	0.03
Male	12 (60)	14 (77.8)	0.31
Body weight (kg)	65.8±9.7	61.4±9.2	0.17
Underlying disease			
CAD	4 (20)	0	0.11
DM	6 (30)	8 (44.4)	0.51
HTN	6 (30)	8 (44.4)	0.51
COPD	0	2 (11.1)	0.22
AKI	3 (15)	3 (16.7)	0.65
Laboratory findings before ECMO support			
White blood cell (10^3/mm^3)	13.96±6.5	13.9±4.5	0.96
Hemoglobin, g/dL	12.5±2.6	11.8±2.5	0.42
Platelets (10^3/mm^3)	209.9±67.2	205.1±52.4	0.81
Total bilirubin (mg/dL)	0.9±1.3	1.2±0.2	0.53
Creatinine (mg/dL)	1.2±0.8	1.3±0.8	0.66
CRP (mg/dL)	3.8±2.3	3.9±5.5	0.91
Clinical conditions before ECMO support			
Pre-ECMO hospital stay (day)	5.2±12.1	1.8±2.3	0.24
Pre-ECMO ICU stay (day)	0.9±0.6	1.0±0.5	0.55
Shock to ECMO time (hour)	4.8±8.5	6.5±7.9	0.13
Clinical outomes during ECMO support			
Duration of ECMO support (day)	8.7±8.6	9.3±6.6	0.81
ECMO time > 7 days	10 (55.6)	14 (70)	0.28
Nosocomial infection during ECMO support	2 (10)	10 (55.6)	< 0.01
Peak value of PCT within first week (pg/dL)	14.7±18.0	66.8±42.2	< 0.01

ECMO: extracorporeal membrane oxygenation, CAD: coronary artery disease, DM: diabetus mellitus, HTN: hypertension, COPD: chronic obstructive lung disease, AKI: acute kidney injury, CRP: C-reactive protein, ICU: intensive care, PCT: procalcitonin. [a]Data are presented as the number of cases (%) for categorical variables or as means±standard deviations for continuous variables.

TABLE 5. Multivariate analysis of risk factors for survival before and during ECMO support

Variables	Adjusted OR (95% CI)	p-value
Age	0.48 (0.32-0.72)	0.56
Nosocomial infection during ECMO support	0.15 (0.01-0.36)	0.2
Peak value of PCT (ng/dL)	1.94 (1.03–3.27)	0.01

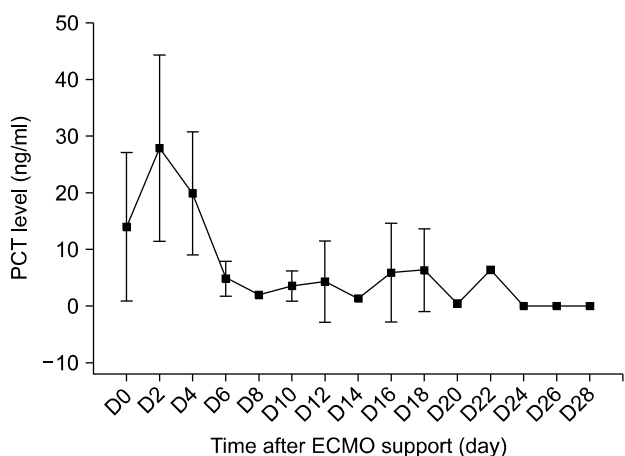ECMO: extracorporeal membrane oxygenation, OR: odds ratio, CI: confidence interval, PCT: procalcitonin.

FIG. 2. Trends of Procalcitonin levels during ECMO support for 28dyas, presented as mean value±standard deviation. Peak value was reached within 48 hours after initiation of ECMO support (mean 25.6±9.4 ng/mL), and decreased to ≤5 ng/mL within 1 week. Mean value of PCT levels after first week varied in diverse patterns, but did not show the high levels shown for the first week. ECMO: extracorporeal membrane oxygenation, PCT: procalcitonin.

3. Association between survival outcome and PCT levels

Fig. 2 shows the trends of PCT (mean values) during ECMO support. Maximal levels were reached within 48 hours after initiation of ECMO support (mean 25.6±9.4 ng/mL), and decreased to ≤5 ng/mL within 1 week. The mean value of PCT levels after the first week varied in diverse patterns, but did not show the high levels shown for the first week. Serial progression of mean PCT levels was compared in the 2 groups during the first week of ECMO support; the mean PCT level was significantly higher in the survival group, according to time (p=0.03) (Fig. 3). In the Kaplan-Meier survival analysis, a PCT level of >10 ng/mL was significantly associated with survival probability within the first week of ECMO support (p=0.01) (Fig 4).

DISCUSSION

We evaluated the trends and predictive value of PCT levels during treatment of adult cardiogenic shock with ECMO, and investigated the role of PCT as a predictor of infection occurrence and clinical outcomes. As it is easy to
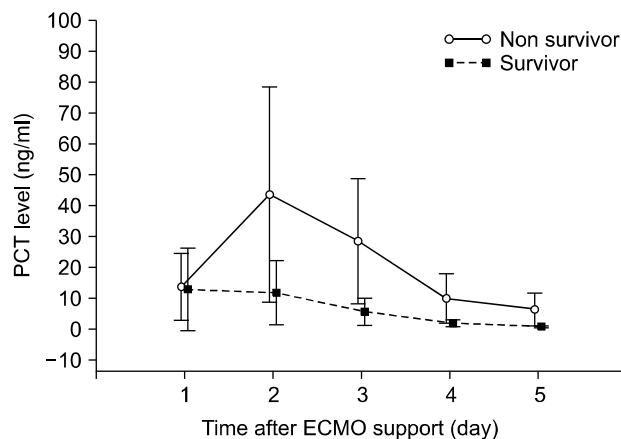
FIG. 3. Comparison between mean PCT levels within 7 days in survivors and non-survivors. Serial progression of mean PCT level was observed during the first week of ECMO support; the mean level was significantly higher over time in the survivor group (p=0.03). ECMO: extracorporeal membrane oxygenation, PCT: procalcitonin.
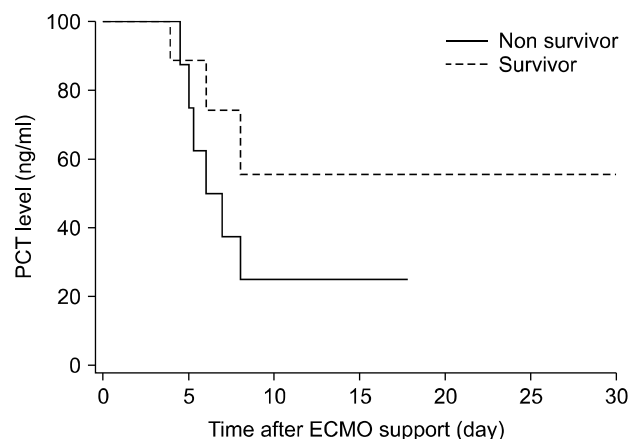

FIG. 4. Kaplan-Meier survival analysis: Peak PCT level ≥10 ng/mL in survivors and non-survivors. PCT level ≥10 ng/mL within the first week of ECMO support was significantly associated with survival probability (p=0.01). ECMO: extracorporeal membrane oxygenation, PCT: procalcitonin.

measure and can be repeatedly checked, PCT has an important role as a predictor of infection. Therefore, many studies have used PCT as a guide to the use of antibiotics, and as a marker to monitor the effectiveness of antibiotic treatment in bacterial lower respiratory tract infections and sepsis.[12-16] PCT is also superior to traditional inflammatory markers such as CRP for diagnosis of bacterial infections.[17-19] In addition, higher PCT levels are associated with disease severity in septic patients.[19] However, many recent studies have shown a negative correlation, suggesting that PCT measurement is not associated with decreased mortality or duration of antibiotic treatment in sepsis.[11,20,21]

Studies on the usefulness of PCT measurement have been performed in various fields. Cardiopulmonary bypass

(CPB), which is essential for cardiac surgery, causes a systemic inflammatory response, and the likelihood of an inflammatory reaction is increased when the running time is prolonged. As acute phase reactions following CPB are associated with organ dysfunction, there is a continuing effort to identify a biomarker for use in early diagnosis of complications after cardiac surgery. It is known that PCT affects the clinical course after cardiac surgery[22] and is a more sensitive indicator than the increase in WBCs or CRP in predicting complications; moreover, the role of PCT is expanding to include prognostic use in specific acute cardiovascular diseases such as aortic dissection.[23] Elevated PCT levels have a negative impact on postoperative complications and outcomes.[16,23] After cardiac surgery, PCT increases if the patient does not enter the recovery phase. Transfusion and deep hypothermia also induce a variety of inflammatory reactions, resulting in an increase in PCT levels during cardiac surgery.[24,25] Thus, it can be inferred that an elevation of PCT in the absence of specific symptoms can predict progressive deterioration. Therefore, PCT measurement after cardiac surgery can enable early detection and intervention to prevent complications. However, its value as a prognostic marker is still unclear due to a lack of evidence. To determine the mechanism by which PCT affects the body, a large-scale, randomized-control trial is needed to evaluate complications after cardiac surgery and to assess the value of other prognostic factors.

Although several studies have attempted to differentiate between increased PCT levels caused by infection versus ECMO, only a few preliminary studies have identified the role of PCT during ECMO therapy, and most have reported PCT as an indicator of infection.[7,8,26] One prospective study in pediatric patients found no correlation between PCT and prediction of infection, but did show that high PCT levels are associated with multi-organ dysfunction.[7] In adults, studies have identified the role of PCT as an indicator of infection during ECMO treatment.[8,26] Our study showed that PCT was a potential serum biomarker for prognosis in patients undergoing ECMO support. Although our study could not precisely identify the change in PCT values correlated with disease severity, we confirmed that a peak value of >10 ng/mL was associated with mortality. However, when we divided patients into 2 groups based on a PCT level of 5 ng/mL, there was no statistically significant difference.

This study has some limitations. Firstly, this was a retrospective analysis of medical records. Thus, a selection bias was not completely excluded because 7.3% of cases were excluded, and association is not equivalent to causation. Second, this single-center study enrolled a relatively small number of patients. In the future, a large-scale, prospective multicenter analysis is required to develop guidelines.

In conclusion, the level of PCT is not useful in prediction of nosocomial infection during ECMO support. However, higher PCT levels within the first week of ECMO are associated with significantly higher mortality.

CONFLICT OF INTEREST STATEMENT

None declared.

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