




## Original Article

# Association between inflammation in acute phase and early onset pneumonia in patients with out-of-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation

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**Background:** Early onset pneumonia (EOP) in patients with cardiac arrest treated with targeted temperature management is a recently debated issue. We assessed the association between C-reactive protein (CRP) levels and development of EOP in patients treated with extracorporeal cardiopulmonary resuscitation (ECPR).

**Methods and Results:** We reviewed the data of all patients admitted to our hospital after out-of-hospital cardiac arrest treated with ECPR between April 2006 and April 2019 who survived for at least 48 h. We collected demographic data, cardiac arrest characteristics, prophylactic antibiotic use, and neurologic outcomes. Diagnosis of EOP was made based on clinical, radiological, and microbiological criteria. The primary endpoint was the association between the incidence of EOP and CRP levels from day 1 to day 4. A total of 55 patients were included, of which 20 developed EOP. CRP levels on days 3 and 4 were significantly elevated in patients who developed EOP (13.1 [11.8–21.1] mg/dL versus 11.6 [7.4–15.2] mg/dL,  $P = 0.005$ ; and 19.0 [16.9–27.1] mg/dL versus 14.7 [7.4–21.2] mg/dL,  $P = 0.019$ , respectively). In the multivariable logistic regression model, the CRP level on day 3 was significantly associated with the development of EOP (odds ratio 1.22; 95% confidence interval 1.06–1.41;  $P = 0.001$ ).

**Conclusions:** Increased inflammation in acute phase was associated with development of EOP in patients treated with ECPR.

**Key words:** C-reactive protein, cardiopulmonary arrest, infection control, inflammation, pneumonia

## INTRODUCTION

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION (ECPR) followed by targeted temperature management (TTM) has shown significant improvement of outcome in patients with out-of-hospital cardiac arrest (OHCA).<sup>1–3</sup> Despite this promising treatment, the condition of systemic inflammatory response, so-called postcardiac arrest syndrome (PCAS), and infectious complications, such as pneumonia, are frequently observed in postresuscitation care.<sup>4–6</sup>

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One previous study reported the relationship between the alteration of C-reactive protein (CRP) levels, inflammatory marker, and early onset pneumonia (EOP) in patients treated with conventional cardiopulmonary resuscitation (CCPR) followed by TTM.<sup>7</sup> In addition, because a recently published randomized controlled trial revealed the benefit of prophylactic antibiotic therapy against pneumonia in patients receiving TTM after OHCA,<sup>4</sup> there has been increasing attention regarding EOP in patients receiving TTM. Although extracorporeal membrane oxygenation (ECMO) has been associated with an increase in inflammatory mediators, such as endotoxins, oxygen-derived free radicals, and cytokines,<sup>8</sup> the association of the alteration of CRP levels with EOP in patients treated with ECPR has never been examined.

In this study, we hypothesized that the higher inflammation in acute phase is associated with the incidence of EOP in patients treated with ECPR. To address this hypothesis, we conducted this observational study and examined the association of CRP levels and the development of EOP in patients treated with ECPR.

## METHODS

### Patients

THIS RETROSPECTIVE STUDY included data from adult patients after OHCA of suspected cardiac origin, treated with ECPR followed by TTM at 34°C and admitted to St. Luke's International Hospital between April 2006 and April 2019. Initial rhythm was assessed by emergency medical service personnel on arrival at the patient's location. The exclusion criterion was death within the first 48 h after admission. The study was approved by the local ethics committee of St. Luke's International Hospital (approval number: 20-R020) and was conducted in accordance with the Declaration of Helsinki.

### ECMO management and postresuscitation care

The patients received standard CPR and post-CA care according to the 2005, 2010, and 2015 American Heart Association guidelines.<sup>9</sup> Before April 2013, the decision to initiate ECPR was made by physicians and cardiologists in emergency departments. From April 2013, patients with OHCA were eligible for ECPR mainly when the following criteria were met: (i) witnessed CA, (ii) shockable initial rhythm, (iii) nonresponder to conventional CPR, and (iv) hospital arrival within 30 min from CA and able to establish ECPR flow within 60 min. ECMO was implanted by well-trained cardiologists and clinical engineers on a sterile field.

We have described the details of ECMO management and postresuscitation care in an intensive care unit in our previous paper.<sup>10</sup> In brief, core temperature was managed by internal cooling by ECMO, and a target core temperature of 34°C was maintained for 24 h, followed by gradual rewarming for the next 24 h. Then, body temperature was maintained at normothermia until 72 h after the return of spontaneous circulation. Weaning of ECMO was usually considered 48 h after the initiation when the patient was hemodynamically stable and adequately oxygenated. Withdrawal of ECMO was considered when there was irreversible multiple organ failure or severe neurologic damage equivalent to brain death, but only after obtaining consent from the patient's relatives.

### Data collection and processing

The following parameters were recorded for each study patient: age, sex, presence of witnessed CA, presence of

bystander CPR, initial rhythm, low flow time, Sepsis-related Organ Failure Assessment (SOFA) score on admission,<sup>11</sup> comorbidities (hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, heart failure, ischemic heart disease, history of percutaneous coronary intervention, history of coronary artery bypass grafting, transient ischemic attack, stroke, asthma, chronic obstructive pulmonary disease, and malignancies), laboratory examination data upon admission (lactate level, white blood cell count, transaminase level), intra-aortic balloon pump and pulmonary artery catheter insertion, prophylactic antibiotic use, intensive care unit length of stay, and neurologic outcomes. The CRP levels were measured every morning from day 1 to day 4. A favorable outcome was defined as a cerebral performance category of 1 or 2, whereas an unfavorable outcome was defined as a cerebral performance category of 3–5.<sup>12</sup> The details of antibiotic use, such as type, dose, and duration, were also recorded.

### Definitions

**Low flow time:** Low flow time was defined as time from collapse to establishment of adequate ECMO flow.

**Prophylactic antibiotic use:** Prophylactic antibiotic use was defined as antibiotic administration within 24 h after admission before presence of any signs of infection.

**EOP:** Diagnosis of EOP was made when the patients met all the clinical, radiological, and microbiological criteria that were acquired after a hospitalization period of >48 h and within 7 days of admission. Clinical criteria were met when the patients showed at least two of three clinical features (i.e., fever  $\geq 38.0^{\circ}\text{C}$ , leukocytosis or leukopenia [ $>12,000$  cells/ $\mu\text{L}$  or  $<4,000$  cells/ $\mu\text{L}$ , respectively], purulent tracheobronchial secretions).<sup>13,14</sup> The radiological criteria were met by the presence of a new or progressive and persistent infiltrate that is characteristic of bacterial pneumonia or the presence of a new consolidation on chest X-ray. The microbiological criteria were met by a positive respiratory culture that did not contain normal bacterial flora. The diagnosis was made by two independent reviewers (DS and TH), who reviewed all the patients' medical charts, laboratory data, and culture results. Disagreements were resolved via discussions.

### Study endpoints

The primary endpoint was the association between the incidence of EOP and CRP levels from day 1 to day 4.

## Statistical analysis

Baseline characteristics were compared using the Wilcoxon rank-sum test for continuous variables and the chi-square test for binary and categorical variables as appropriate. Univariate and multivariate logistic regression analyses were performed for the primary endpoints. Multivariate analysis was adjusted for possible confounders (age, low flow time, prophylactic antibiotic use, CRP level on day 3, SOFA score on admission).<sup>15,16</sup> The ability of the CRP level on day 3 to predict EOP was evaluated using the receiver operating characteristic analysis, with the areas under the curves showing the highest sensitivity. Statistical analysis was performed using JMP version 14 statistical software (SAS Institute, Inc., Cary, NC, USA). Missing data were excluded from the analysis.

## RESULTS

FROM APRIL 2006 to April 2019, a total of 73 OHCA patients of suspected cardiac origin were treated with ECPR in our hospital. Of these, 18 patients were excluded because of death within 48 h of admission. The remaining 55 patients were enrolled in analysis, and 20 patients developed EOP (Fig. 1).

### Baseline characteristics of the study population

Overall, median patient age was 55 years, and 95% were male. The median low flow time was 51 min. Prophylactic antibiotics were used for 73% of the patients. Favorable neurologic outcomes were observed in 33% of patients. The baseline characteristics were compared between patients with and without EOP, and there were no significant differences between the groups (Table 1).

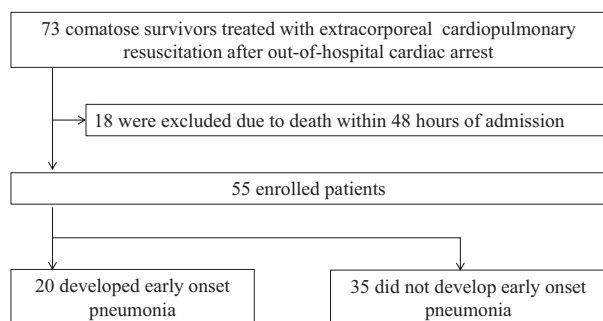


Fig. 1. Patient flow.

## Association between EOP and CRP levels

Most patients were diagnosed with EOP on day 4 ( $n = 12$ ; Fig. 2). The CRP levels on day 1 and day 2 were not significantly different between the groups; however, the CRP levels on day 3 and day 4 were progressively elevated in patients who developed EOP (median [interquartile range], 13.1 [11.8–21.1] mg/dL versus 11.6 [7.4–15.2] mg/dL,  $P = 0.005$ ; and 19.0 [16.9–27.1] mg/dL versus 14.7 [7.4–21.2] mg/dL,  $P = 0.019$ , respectively; Fig. 3). The area under the receiver operating characteristic curve of the CRP level on day 3 for predicting EOP was 0.696 ( $P = 0.012$ ; Fig. 4).

## Primary analysis

In the multivariable logistic regression model, CRP level on day 3 was significantly associated with the development of EOP (odds ratio 1.22; 95% confidence interval 1.06–1.41,  $P = 0.001$ , Table 2).

## Details of antibiotic use

Prophylactic antibiotics were used in 73% of the patients. Among these, 90% were treated with ampicillin–sulbactam. Other antibiotics, such as cefazolin, levofloxacin, and clindamycin, were also used in some cases. In most cases, ampicillin–sulbactam was used with a renal-adjusted dosage of 1.5 g every 6–8 h. The median duration of the antibiotic use was 9 days.

## Subgroup analysis

Subgroup analysis was performed in patients who received prophylactic antibiotics, and CRP level on day 3 was significantly associated with the development of EOP (odds ratio 1.21; 95% confidence interval 1.03–1.41,  $P = 0.019$ ; Table S1).

## DISCUSSION

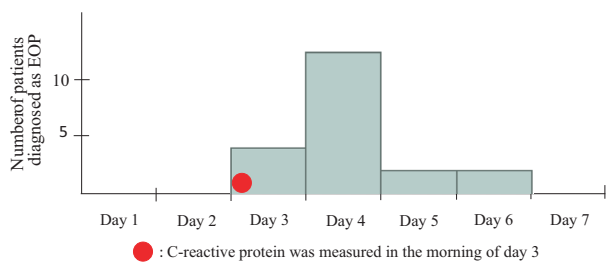
IN THIS OBSERVATIONAL study, CRP levels on day 3 and day 4 were significantly elevated in patients with EOP compared with patients without EOP. In the multivariable logistic regression model, CRP levels on day 3 were an independent predictor of developing EOP. Subgroup analysis also showed significant association between CRP levels on day 3 and EOP development in patients who received prophylactic antibiotics.

**Table 1.** Baseline characteristics<sup>†</sup>

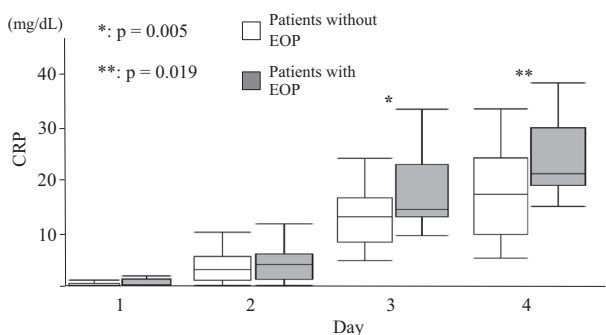
Variables	Total (N = 55)	Patients with EOP (N = 20)	Patients without EOP (N = 35)	P-value
Age (years)	55 (42–65)	61 (51–66)	55 (38–62)	0.451
Male sex	52 (94.5)	19 (95.0)	33 (94.3)	0.911
Witnessed cardiac arrest	53 (96.4)	19 (95.0)	34 (97.1)	0.683
Bystander CPR	41 (74.5)	17 (85.0)	24 (68.6)	0.178
Initial rhythm				
Vf	44 (80.0)	14 (70.0)	30 (85.7)	0.229
VT	0 (0)	0 (0)	0 (0)	
PEA	10 (18.2)	5 (25.0)	5 (14.3)	
Asystole	1 (1.8)	1 (5.0)	0 (0)	
Shockable rhythm (%)	44 (80.0)	14 (70.0)	30 (85.7)	0.161
Low flow time (min)	51 (42–63)	52 (31–64)	51 (45–61)	0.478
SOFA score on admission	12 (11–13)	12 (11–13)	12 (11–13)	0.385
Comorbidities				
Hypertension	18 (32.7)	9 (45.0)	9 (25.7)	0.146
Diabetes mellitus	13 (23.6)	4 (20.0)	9 (25.7)	0.628
Hyperlipidemia	6 (10.9)	3 (15.0)	3 (8.6)	0.469
Chronic kidney disease	4 (7.3)	2 (10.0)	2 (5.7)	0.556
Heart failure	5 (9.1)	2 (10.0)	3 (8.6)	0.859
Ischemic heart disease	6 (10.9)	2 (10.0)	4 (11.4)	0.870
History of PCI	4 (7.3)	1 (5.0)	3 (8.6)	0.623
History of CABG	0 (0)	0 (0)	0 (0)	
TIA, stroke	1 (1.8)	1 (5.0)	0 (0)	0.182
Asthma, COPD	1 (1.8)	0 (0)	1 (2.86)	0.446
Malignancy	2 (3.6)	0 (0)	2 (5.7)	0.276
No past medical history	3 (5.5)	2 (10.0)	1 (2.9)	0.261
Lactate (mmol/L)	13.9 (10–17)	11.7 (7.9–17.0)	11.5 (9.1–17.0)	0.155
WBC (10 <sup>3</sup> /μL)	11.3 (8.6–14.5)	10.3 (7.4–14.7)	11.4 (8.8–14.4)	0.572
AST (U/L)	95 (49–199)	92 (46–193)	123 (51–204)	0.496
ALT (U/L)	76 (44–176)	54 (39–180)	89 (45–182)	0.761
ECPR duration (days)	4 (3–7)	5 (3–7)	4 (3–6)	0.959
IABP support (%)	49 (89.1)	17 (85.0)	32 (91.4)	0.462
IABP duration (days)	5 (4–8)	6 (3–8)	5 (4–8)	0.679
PAC (%)	50 (90.1)	19 (95.0)	31 (88.6)	0.425
PAC duration (days)	5 (4–8)	6 (4–8)	5 (4–8)	0.897
Prophylactic antibiotics use (%)	40 (72.7)	16 (80.0)	24 (68.6)	0.360
ICU LOS (days)	16 (10–23)	15 (8–24)	16(11–24)	0.974
Outcome				
CPC1 (%)	10 (18.2)	4 (20.0)	6 (17.1)	0.336
CPC2 (%)		8 (40.0)	5 (14.3)	3 (8.6)
CPC3 (%)	8 (14.5)	3 (15.0)	5 (14.3)	
CPC4 (%)	0 (0)	0 (0)	0 (0)	
CPC5 (%)	29 (52.7)	8 (40.0)	21 (60.0)	
Favorable neurological prognosis (%)	18 (32.7)	9 (45.0)	9 (25.7)	0.143

ALT, alanine aminotransferase; AST, aspartate transaminase; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; EOP, early onset pneumonia; IABP, intra-aortic balloon pumping; ICU, intensive care unit; LOS, length of stay; PAC, pulmonary artery catheter; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; SOFA, sequential organ failure assessment; TIA, transient ischemic attack; Vf, ventricular fibrillation; VT, ventricular tachycardia; WBC, white blood cell.

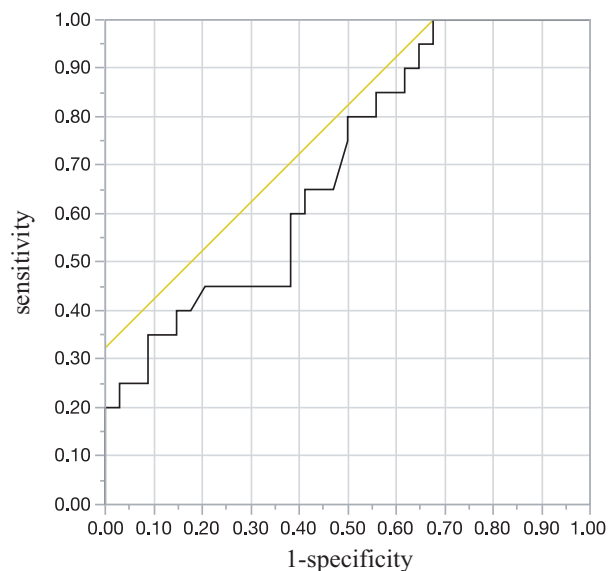
<sup>†</sup>Data are presented as median (interquartile range) for continuous variables and *n* (%) for categorical variables.



**Fig. 2.** Histogram of patients diagnosed with early onset pneumonia (EOP).  
● : C-reactive protein was measured in the morning of day 3



**Fig. 3.** C-reactive protein (CRP) levels of patients with and without early onset pneumonia (EOP).



**Fig. 4.** Receiver operating characteristic curve of C-reactive protein level on day 3 for predicting early onset pneumonia.

## Comparison

In a previous study, which examined CA patients who received CCPR, median CRP levels were 14 mg/dL on day 3 and 16 mg/dL on day 4.<sup>17</sup> In our current study, which examined 55 CA patients who received ECPR, CRP levels were 12.4 mg/dL (interquartile range 9.4–16.5 mg/dL) on day 3 and 18.2 mg/dL (interquartile range 11.9–21.9 mg/dL) on day 4. A simple comparison cannot be obtained because of the difference in patients populations; however, CRP levels on day 3 and day 4 in this study were almost the same value as in the previous study which examined patients treated with CCPR. In addition, several studies compared CRP levels between patients with and without pneumonia treated with CCPR.<sup>7,18</sup> Although the medians or means of CRP were not described, alternations of CRP levels on day 3 and day 4 were the same as in our current study.

## Mechanism

CRP is a pentameric protein produced mainly by hepatocytes driven by interleukin-6.<sup>19</sup> CRP is widely used in routine clinical practice and plays an important role in diagnosing new infection; however, CRP levels also elevate other clinical conditions such as systemic inflammatory response. PCAS comprises anoxic brain injury, myocardial dysfunction, systemic ischemia/reperfusion response following CA, and is associated with increased endotoxins, oxygen-derived free radicals, and cytokines.<sup>20</sup> In patients with CA, severity of PCAS is associated with length of no flow and low flow times. Generally, patients treated with ECPR have longer low flow time than those treated with CCPR, so higher inflammation can be induced in patients treated with ECPR.<sup>21</sup> In addition, extracorporeal circulation itself induces systemic inflammation due to the exposure of a patient's blood to the nonendothelialized surface of the ECMO circuit.<sup>8</sup> By contrast, initiation of extracorporeal flow can provide systemic organ perfusion and has a potential to suppress inflammation. A previous study reported ECPR increased coronary perfusion compared with CCPR.<sup>22</sup> Another study revealed that ECPR treatment decreased multiple inflammatory factors (tumor necrosis factor alpha, interleukin-1, and interleukin-6) compared with CCPR.<sup>23</sup> ECPR is able to provide effective blood circulation and gas exchange in the absence of patients own cardiopulmonary circulation. Therefore, ECPR treatment can stop acute ischemia and hypoxia in organs, and decrease ischemia-reperfusion injury. Our study showed the same CRP levels compared with the previous study that examined patients treated with CCPR, and the result can be explained by the

**Table 2.** Unadjusted and adjusted associations between incidence of EOP and CRP levels

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
CRP level on day 3	1.15 (1.03–1.28)	0.005	1.22 (1.06–1.41)	0.001
Age	1.01 (0.97–1.05)	0.441	0.99 (0.94–1.03)	0.671
SOFA score on admission	1.18 (0.81–1.72)	0.382	1.60 (0.92–2.78)	0.065
Prophylactic antibiotic use	1.83 (0.50–6.77)	0.034	3.36 (0.65–17.21)	0.123
Low flow time	0.98 (0.95–1.01)	0.963	0.95 (0.91–1.00)	0.024

CI, confidence interval; CRP, C-reactive protein; EOP, early onset pneumonia; OR, odds ratio; SOFA, sequential organ failure assessment.

supposition that ECPR has both factors that increase and decrease inflammation markers in CA patients.

### Clinical implementation

This study revealed that elevated inflammation in acute phase is associated with the development of EOP in patients treated with ECPR. Routine follow-up of CRP might help us with early detection and diagnosis of pneumonia in postresuscitation care.

### Limitations

Several limitations should be addressed in this study. First, we evaluated only CRP levels in this study, and other inflammation markers such as interleukin-6 and procalcitonin should be examined. Second, the number of patients in this study was relatively low. For example, our study showed that prophylactic antibiotic use is not associated with the incidence of EOP, but we believe this to be a beta error because of the low sample size. Third, the diagnostic criteria of pneumonia were partially subjective. Pulmonary edema and contusion were difficult to distinguish from infiltration of pneumonia in chest X-ray.

### CONCLUSION

**I**NCREASED IN flammation in the acute phase is associated with the development of EOP in patients treated with ECPR.

### ACKNOWLEDGEMENTS

**N**ONE.

### DISCLOSURE

Approval of the research protocol: N/A.

Informed Consent: N/A.

Registry and the Registration No. of the study/Trial: N/A.

Animal Studies: N/A.

Conflict of interest: None declared.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Table S1.** Subgroup analysis of the association between the incidence of pneumonia and CRP levels.