Levels of Catecholamines in the Plasma of Patients with Cardiopulmonary Arrest

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Summary

So far, there remains a controversy regarding the efficacy of epinephrine (Ep) in patients with cardiopulmonary arrest (CPA). In this study, we evaluated the importance of the plasma levels of catecholamines prior to the administration of Ep in patients with CPA. Patients with out-of-hospital cardiac arrest (OHCA) who were transferred to Gunma University Hospital were enrolled prospectively between July 2014 and July 2017. The levels of catecholamines [Ep, norepinephrine (NEp), and dopamine] and vasopressin (antidiuretic hormone) in the plasma were measured using blood samples of cardiogenic patients with OHCA not treated with Ep. Patients were divided into two groups: the return of spontaneous circulation [ROSC(+) group and the no return of spontaneous circulation [ROSC(−)] group. The plasma levels of these agents and the conditions of resuscitation were compared between these two groups. 48 patients with cardiogenic CPA had not been treated with Ep prior to obtaining the blood samples. The ROSC(+) and ROSC(−) groups included 14 and 34 patients, respectively. The frequency of prehospital defibrillation was significantly higher in the ROSC(+) group. However, the prehospital resuscitation time was significantly shorter in the ROSC(+) group. Moreover, the levels of Ep and NEp in the plasma were significantly lower in the ROSC(+) group. The increased levels of Ep in the plasma may not be associated with the acquisition of ROSC in patients with cardiogenic CPA.

Key words: Cardiopulmonary resuscitation, Epinephrine

So far, there remains a controversy regarding the efficacy of epinephrine (Ep) in patients with cardiopulmonary arrest (CPA). In 2009, a randomized study showed that treatments including Ep did not provide an overall survival benefit.1 In 2012, Hagihara, et al. reported that Ep is associated with a lower likelihood of long-term survival in a large observational study.2 Although the efficacy of Ep in patients with CPA has been reported,3,4 these studies did not address critical outcomes such as survival to discharge and survival to discharge with good neurological outcomes using either vasopressors or antiarrhythmic drugs in such patients. A weak recommendation by the 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations, based on low-quality evidence, suggested that standard-dose Ep be administered to patients with CPA.5,6 Recently, Perkins, et al. performed a randomized trial of Ep in out-of-hospital cardiac arrest (OHCA) and reported that the use of Ep resulted in a significantly higher rate of 30-day survival compared to the use of placebo. However, there was no significant between-group difference in the rate of favorable neurological outcomes in adults with OHCA because more survivors had severe neurological impairments in the Ep group.6

A correlation between the levels of catecholamines such as Ep, norepinephrine (NEp), and dopamine (DOA) in the plasma and prognosis in patients with CPA may be useful for determining the efficacy of Ep during cardiopulmonary resuscitation (CPR). The purpose of this study was to evaluate the importance of the levels of the aforementioned catecholamines and vasopressin in the plasma prior to the administration of Ep in patients with CPA.

Methods

This was a prospective, observational, clinical study, approved by the ethics committee of Gunma University Hospital (IRB #14-13). Written informed consent was provided by the relatives of the patients with CPA at the time of transfer to Gunma University Hospital.

Patients with OHCA who were transferred to Gunma University Hospital between July 2014 and July 2017 were included. CPR was required in all patients. The levels of catecholamines such as Ep, NEp, and DOA in the plasma were measured using blood samples obtained im-
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Figure 1. Study flowchart. CPA indicates cardiopulmonary arrest; Ep, epinephrine; ROSC(+), return of spontaneous circulation; and ROSC(−), no return of spontaneous circulation.

Immediately upon arrival to the hospital. In addition, the level of vasopressin [antidiuretic hormone (ADH)] in the plasma was measured. In this study, we did not measure the exact time between the arrival at the hospital and blood sampling. Blood samples were centrifuged and the serum was stored at −80°C. The levels of catecholamines and ADH were measured using high-performance liquid chromatography and radioimmunoassay, respectively (Bio-Medical Laboratories Inc., Tokyo, Japan).

CPR was performed in conformity with the resuscitation guidelines established in 2015 by the Japan Resuscitation Council. Successful resuscitation [i.e., return of spontaneous circulation, ROSC(+)] was defined as the detection of a pulse at the carotid artery, femoral artery, or radial artery under advanced CPR, as well as subsequent maintenance of systolic blood pressure above or at 80 mmHg for at least one hour with or without the administration of vasoconstrictive agents. Patients who did not achieve the above were defined as ROSC(−).

Patients in whom Ep was already administered prior to obtaining blood samples for the measurement of catecholamines were excluded. Moreover, patients under 18 years of age were excluded (Figure 1). Patients not treated with Ep prior to blood sampling, in whom the cause of CPA was cardiogenic, were extracted and divided into two groups, namely, the ROSC(+) and ROSC(−) groups. The levels of the aforementioned catecholamines and ADH, as well as the conditions of resuscitation prior to and after arrival at the hospital, were compared between these two groups.

Statistical analysis: The IBM SPSS Statistics 25 software (IBM Japan, Tokyo, Japan) was used for statistical analyses. Data are shown as number or median. The Mann-Whitney U, chi-squared, and Fisher’s exact tests were used to conduct comparisons between the ROSC(+) and ROSC(−) groups. In addition, Pearson’s correlation analysis was also used to evaluate the relation between the levels of catecholamines and ADH and the time from the contact to CPA patients by emergency services to arriving at the hospital. $P < 0.05$ denoted statistical significance.

Results

A total of 298 patients with OHCA were transferred to our hospital between July 2014 and July 2017. Blood samples were obtained from 170 patients. Of those, 65 patients already treated with Ep prior to their arrival at our hospital were excluded. Among the remaining 105 patients, 48 had cardiogenic CPA and were not treated with Ep prior to blood sampling (Figure 1).

In 41 patients, blood samples were obtained during CPR at the hospital. The remaining seven patients achieved ROSC prior to their arrival at the hospital. In those seven patients, CPR was performed in a prehospital situation in approximately 10 minutes on average, and the time between ROSC and obtaining the blood samples was
The median age among the selected 48 patients was 81 years, and the majority were males (26 patients). The ROSC(+) and ROSC(−) groups included 14 and 34 patients, respectively.

The Table shows comparisons between the two groups in terms of resuscitation prior to and after arrival at the hospital. There were no significant differences between the two groups in terms of age, male-to-female ratio, and the execution rate of bystander CPR. The proportion of patients with ventricular fibrillation was significantly larger in the ROSC(+) group than in the ROSC(−) group. Therefore, the frequency of prehospital defibrillation was significantly higher in the ROSC(+) group than in the ROSC(−) group. However, the proportion of patients with asystole was significantly larger in the ROSC(−) group than in the ROSC(+) group. Of note, the prehospital resuscitation time was significantly shorter in the ROSC(+) group than in the ROSC(−) group. Furthermore, the resuscitation time after arrival at the hospital and the total resuscitation time were significantly shorter in the ROSC(+) group than in the ROSC(−) group.

The levels of catecholamines and ADH in the plasma are shown in Figures 2 and 3. As shown in Figure 2A, the level of Ep in the plasma prior to the administration of Ep was significantly lower in the ROSC(+) group than in the ROSC(−) group (0.34 versus 2.28 ng/mL, respectively; \( P = 0.002 \)). In addition, the level of NEp in the plasma was significantly lower in the ROSC(+) group than in the ROSC(−) group (0.49 versus 1.53 ng/mL, respectively; \( P = 0.007 \)) (Figure 2B). The level of DOA in the plasma was numerically lower in the ROSC(+) group than in the ROSC(−) group (0.05 versus 0.10 ng/mL, respectively; \( P = 0.120 \)) (Figure 3A). There was no significant difference in the level of ADH in the plasma between the ROSC(+) and the ROSC(−) groups (42.7 versus 10.2 pg/mL, respectively; \( P = 0.504 \)) (Figure 3B).
The correlations between the levels of catecholamines and ADH and the time from the contact to CPA patients by emergency services to arriving at the hospital were hardly found [Ep: correlation coefficient (CC): 0.154, \( P = 0.377 \); NEp: CC: 0.273, \( P = 0.107 \); DOA: CC: 0.196, \( P = 0.252 \); ADH: CC: \(-0.136, P = 0.360\), respectively].

Discussion

In 1983, Tárnoky, et al.10) evaluated the relationship between the levels of catecholamines and survival in subjects with hemorrhagic shock using animal models. They reported that the levels of catecholamines (i.e., Ep and NEp) in the plasma were significantly higher in the non-surviving animals. In those animals, extremely high levels of catecholamines represented the stage of shock irreversibility.

In the present study, we showed that the levels of catecholamines and ADH measured in blood samples prior to the administration of Ep in patients with cardiogenic CPA were higher than normal in both the ROSC(+) and the ROSC(−) groups. In addition, the plasma levels of Ep and NEp prior to the administration of Ep were significantly lower in the ROSC(+) group than in the ROSC(−) group. Moreover, the duration of prehospital CPR was significantly shorter in the ROSC(+) group than in the ROSC(−) group. Prehospital defibrillation was not performed in any patient from the ROSC(−) group. The dosage of Ep and resuscitation time after arrival at the hospital were significantly lower and significantly shorter, respectively, in the ROSC(+) group. This time was longer in our study (18.2 minutes, mean) versus the previous study (8.0 minutes, mean). (2) The method used for the measurement of catecholamine levels (high-performance liquid chromatography) was identical in both studies. However, it may be different in terms of the testing precision. (3) There are differences in the guidelines for CPR. Despite these differences, our results are consistent with those of this previous study. In addition, the investigators of the previous study valuably reported the plasma level of Ep after the administration of Ep. They showed that the plasma level of Ep increased approximately 10 times after the administration of 1 mg Ep in both the ROSC(+) and the ROSC(−) groups.

In 1963, Redding, et al.12-14) described the benefit of Ep in CPA using animal models and illustrative cases. In addition, Otto, et al. studied the mechanism of action of Ep during resuscitation after CPA. Traystman, et al. reported that the administration of Ep was particularly effective in sustaining cerebral and coronary perfusion dur-
ing CPR in animal experimental models. \cite{18-20} Kornberger, \textit{et al.} \cite{21} also reported that the coronary perfusion pressure was significantly higher after the administration of Ep in a pig model of hypothermic cardiac arrest and closed-chest CPR.

On the other hand, the toxicity of catecholamines (including Ep) has also been reported. Catecholamines have been shown to be associated with cardiotoxicity, and thus the administration of Ep may affect the myocardium. Berg, \textit{et al.} revealed that the administration of high-dose Ep did not improve the survival rate or neurological outcome in animal experimental models. \cite{22,23} Moreover, they insisted that high-dose Ep resulted in severe tachycardia, hypertension, and a higher mortality rate immediately after resuscitation. \cite{24} Wittstein, \textit{et al.} \cite{25} compared the levels of catecholamines (EP, NEp, and DOA) in the plasma between a group of 13 patients with Takotsubo cardiomyopathy and a group of seven patients hospitalized for acute myocardial infarction (Killip class III). They reported that the levels of catecholamines in the plasma of patients with Takotsubo cardiomyopathy were two- to three-fold higher than those observed in patients with myocardial infarction. The histological changes in the myocardium observed in patients with Takotsubo cardiomyopathy were similar to those observed in catecholamine-induced cardiotoxicity in both animals \cite{26} and humans. \cite{27} These changes, which differ from those of ischemic cardiac necrosis, include contraction band necrosis, neutrophil infiltration, and fibrosis. These findings may reflect consequences of high intracellular levels of Ca\textsuperscript{2+}. It has been proposed that an overload of Ca\textsuperscript{2+} in myocardial cells may be responsible for the ventricular dysfunction observed in catecholamine-induced cardiotoxicity. \cite{28}

Recently, Katsumi, \textit{et al.} reported that catecholamine-induced senescence of endothelial cells and bone marrow cells played a pivotal role in the progression of heart failure using mouse models. \cite{29}

Furthermore, there are some reports suggesting that Ep results in excessive vasoconstriction of vascular beds, limiting cerebral blood flow and oxygen delivery. Consequently, the administration of Ep may exert a negative effect on the cerebral blood flow. In animal studies of cardiac arrest, the administration of Ep decreased the cerebral capillary blood flow \cite{29-30} and cerebral cortical oxygen tension. \cite{30} Deakin, \textit{et al.} \cite{31} reported the first clinical evidence demonstrating the effects of Ep on cerebral oxygenation (rSO\textsubscript{2}) during CPR. The findings suggested that a bolus of 1 mg Ep administered intravenously during CPR produced a small and clinically insignificant increase in rSO\textsubscript{2}; 5 minutes after administration. In addition, clinical studies raised concerns that Ep may fail in improving the overall survival and, specifically, neurologically intact survival after CPR. \cite{29,30} It is possible that excessive and unnecessary administration of Ep adversely affects the cerebral circulation and neurological prognosis in patients with CPA.

DOA is converted into NEp by dopamine \(\beta\)-hydroxylase; \cite{33} therefore, DOA is a precursor of NEp and Ep. In the present study, the level of DOA in the plasma was lower in the ROSC(+) group than in the ROSC(−) group. However, the difference was not statistically significant. The reason for this difference is unclear, and the metabolism of DOA (including the activity of dopamine \(\beta\)-hydroxylase and DOPA decarboxylase, which play a role in converting DOPA into DOA) may be associated. \cite{34,35}

Mukoyama, \textit{et al.} \cite{36} conducted a randomized, controlled study comparing multiple doses of standard-dose Ep with multiple doses of standard-dose vasopressin after OHCA in the emergency department. They concluded that repeated injections of either vasopressin or Ep during prolonged advanced cardiac life support resulted in comparable survival. On the other hand, a weak recommendation by the 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations, based on low-quality evidence, suggested that Ep should be used instead of vasopressin in patients with cardiac arrest. \cite{37} Moreover, in the present study, there was no significant difference in the plasma level of ADH between the ROSC(+) group and the ROSC(−) group.

The limitations of this study must be acknowledged. This was a single-center study that comprised a small number of patients. Only patients with cardiogenic CPA were included in this study. We attempted to obtain the blood samples from patients immediately or as soon as possible after arrival at the hospital. However, we did not have accurate information regarding the time of blood sampling. The levels of catecholamines in the plasma were determined using a single measurement, and no sequential assessment of those levels was performed. Further studies are warranted to evaluate the usefulness of Ep administration during CPR.

**Conclusions**

The levels of Ep and NEp in the plasma of patients with cardiogenic CPA, not treated with a prehospital administration of Ep, were significantly lower in patients with ROSC. Increased levels of Ep in the plasma may not be associated with the acquisition of ROSC in patients with cardiogenic CPA.

**Disclosures**

**Conflicts of interest:** The authors have no conflicts of interest to declare.

**References**


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