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Research Article

Prospective Investigation on The Significance of Carboxyhemoglobin Level in out-of-Hospital Cardiopulmonary Arrest

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Abstract

Purpose: This study prospectively investigated the significance of the level of carboxyhemoglobin following an out of hospital (OH) cardiopulmonary arrest (CPA).

Methods: Patients who were transported to this department due to an OH CPA from April 2013 to March 2014 were included in the study. The subjects were divided into two groups based on their ability to achieve the return of spontaneous circulation and those who were not (ROSC+ vs. ROSC-).

Results: One hundred eight patients were included as subjects in this study (ROSC-, n=64; ROSC+, n=44). There were no significant differences associated with sex, age or the frequency of bystander CPR between the two groups; while the frequency of witnessed collapse, frequency of ventricle fibrillation at the scene, pH level and the base excess were significantly higher in the ROSC+ group than in the ROSC- group. The level of lactate in the ROSC+ group was lower than that in the ROSC- group. While the level of carboxyhemoglobin in the ROSC+ group was higher than that in the ROSC- group, the difference was not significant (p=0.06). The time course of carboxyhemoglobin level changes was investigated in 35 subjects. The average 2nd level of carboxyhemoglobin tended to significantly increase in comparison with the 1st level in the ROSC+ group, while the average 2nd level of carboxyhemoglobin tended to significantly decrease in the ROSC- group (p<0.05).

Conclusion: There might be an association between carboxyhemoglobin level and ROSC, given that the level of carboxyhemoglobin tended to increase after ROSC.

Keywords: Cardiopulmonary Arrest; Carboxyhemoglobin; Outcome; Circulation

Introduction

Global cerebral ischemia-reperfusion injury induces the expression of Heme oxygenase 1 (HO-1) [1]. HO-1 is a ubiquitous inducible stress-response protein which serves a major metabolic function in heme turnover. HO-1 activity cleaves heme to form biliverdin-IX α , endogenous carbon monoxide

(CO), and iron, which play a concerted role in cytoprotection against oxidative stress and in the modulation of cell proliferation and differentiation [2,3]. At low concentrations, exogenous CO can confer cyto- and tissue-protective effects similar to those associated with endogenous HO-1 expression, including antioxidative, anti-inflammatory, antiproliferative, and antiapoptotic effects [4]. In addition, blood car-

carboxyhemoglobin is an indicator of the endogenous production of CO by HO-1 and exogenous inhaled CO [5]. Yanagawa, one of co-authors of this study previously reported that the average value of carboxyhemoglobin in patients regaining consciousness from out of hospital (OH) cardiopulmonary arrest (CPA) was greater than the value in other patients, and suggested that the level of carboxyhemoglobin on arrival might be an important prognostic factor regarding the clinical outcome of OH CPA patients [6]. This study therefore prospectively investigated the significance of the level of carboxyhemoglobin following an OH CPA.

Methods

This prospective study was approved by the Institutional Review Board of Juntendo University (?) and obtained approval number 000011008 in the UMIN Clinical Trials Registry. Patients who were transported to this department due to an OH CPA from April 2013 to March 2014 were included in the study. The exclusion criteria included patients who did not undergo blood gas analysis on arrival or who experienced a CPA due to acute carbon monoxide intoxication or trauma. The subjects were divided into two groups based on their ability to achieve the return of spontaneous circulation and those who were not able to achieve the return of spontaneous circulation (ROSC+ vs. ROSC-). The following data of the two groups were analyzed: age, sex, the occurrence of witnessed collapse, the performance of cardiopulmonary resuscitation (CPR) by a bystander (bystander CPR), initial electrocardiography at scene, the level of carboxyhemoglobin on arrival, and the patient's category of cerebral performance after one month. The time course of the changes of carboxyhemoglobin levels was also analyzed if subjects underwent multiple blood gas analyses during resuscitation in the emergency room. This hospital has been able to analyze serum carboxyhemoglobin and methemoglobin levels using a blood gas analyzer (ABL 520 Radiometer^R, Copenhagen, Denmark) since 2005.

Both the chi-squared test and Student's *t*-test were used for the statistical analyses. A *p* value of less than 0.05 was considered to be statistically significant. A multivariate logistic regression analysis was performed to separately evaluate the independent factors associated with ROSC. The variables included in the multivariate analysis were those with significance levels of *p*<0.05 based on a univariate analysis and the level of carboxyhemoglobin on arrival. The odds ratio and the corresponding 95% confidence intervals were also calculated. Data are represented as the mean ± standard error.

Results

A total of 169 patients were transported to this department due to OH CPA during the target period. Among them, 37 patients were excluded due to trauma. There were no cases of OH CPA due to carbon monoxide intoxication. There were 24

patients who did not undergo blood gas analysis on arrival because they were under the category of do not resuscitate (end stage of cancer, the existence of rigor mortis, or the will expressed personally by the patient or his or her kin). The remaining 108 patients were included as subjects in this study (ROSC-, *n*=64; ROSC+, *n*=44).

The results of the groups defined by their ROSC statuses are summarized in Table 1. There were no significant differences associated with sex, age or the frequency of bystander CPR between the two groups; while the frequency of witnessed collapse, frequency of ventricle fibrillation at the scene, pH level and the base excess were significantly higher in the ROSC+ group than in the ROSC- group. The level of lactate in the ROSC+ group was lower than that in the ROSC- group. While the level of carboxyhemoglobin in the ROSC+ group was higher than that in the ROSC- group, the difference was not significant (*p*=0.06). There were six survivors among the ROSC+ group, 5 of whom achieved social rehabilitation, while one acquired a severe level of disability. An additional statistical analysis between the surviving and non-surviving patients was performed, however, there was no significant change observed in the level of carboxyhemoglobin.

Table 1. Results based on the return or the lack of return of circulation

	ROSC- n = 64	ROSC + n = 44	<i>P</i> value
Sex (Male/Female)	38/26	33/11	n.s.
Age	72.1 ± 2.3	68.7 ± 2.5	n.s.
Witnessed collapse	19 (42.2%)	24 (54.5 %)	<0.05.
Bystander cardiopulmonary resuscitation	30 (46.8%)	25 (56.8%)	n.s.
Ventricular fibrillation at scene	1 (1.5%)	9 (20.4%)	0.001.
pH	6.81 ± 0.02	7.02 ± 0.03	<0.0001
Base excess on arrival (mmol/l)	-21.1 ± 1.0	-14.2 ± 1.3	<0.0001
Lactate on arrival (mg/dl)	16.9 ± 0.7	11.6 ± 0.9	<0.0001
Carboxyhemoglobin (%)	0.54 ± 0.07	0.80 ± 0.13	0.06
Clinical performance category	5	4.5 ± 0.1	<0.01

ROSC: return of spontaneous circulation

ROSC+: ROSC achieved

ROSC-: ROSC not achieved

n.s.: not significant

The results are expressed as the mean ± SE

A multivariate logistic regression analysis was performed to

evaluate the independent factors affecting the outcome by univariate analysis using significant results (occurrence of witnessed collapse, ECG at scene, pH, base excess, lactate) and by the level of carboxyhemoglobin. As a result, ECG at scene (odds ratio, 0.106; 95% confidence interval, 0.012-0.922; $p < 0.05$) was found to be a factor independently associated with ROSC positivity.

Table 2. Trends of the 2nd value of carboxyhemoglobin in ROSC+ and ROSC- patients

	Control n = 13	ROSC + n = 22	P value
Sex (Male/Female)	8/5	17/5	n.s.
Age	65.0 ± 3.6	61.4 ± 3.2	n.s.
Witnessed collapse	5 (38.4%)	11 (50.0%)	n.s.
Bystander cardiopulmonary resuscitation	7 (53.8%)	12 (54.5%)	n.s.
Ventricular fibrillation at scene	0	5 (%)	n.s.
Carboxyhemoglobin 1 st (%)	0.79 ± 0.27	0.70 ± 0.11	n.s.
Carboxyhemoglobin 2 nd (%)	0.70 ± 0.24	1.00 ± 0.17	n.s.
Number of increased value at 2 nd analysis	3 (23.0%)	15 (68.1%)	0.01

ROSC: return of spontaneous circulation

ROSC+: ROSC achieved

ROSC-: ROSC not achieved

n.s.: not significant

The results are expressed as the mean ± SE

The time course of carboxyhemoglobin level changes was investigated in 35 subjects. The background information of these 35 subjects is shown in **Table 2**. There was no statistical difference between the two groups. However, the average 2nd level of carboxyhemoglobin tended to significantly increase in comparison with the 1st level in the ROSC+ group, while the average 2nd level of carboxyhemoglobin tended to significantly decrease in comparison with the 1st level in the ROSC- group ($p < 0.05$).

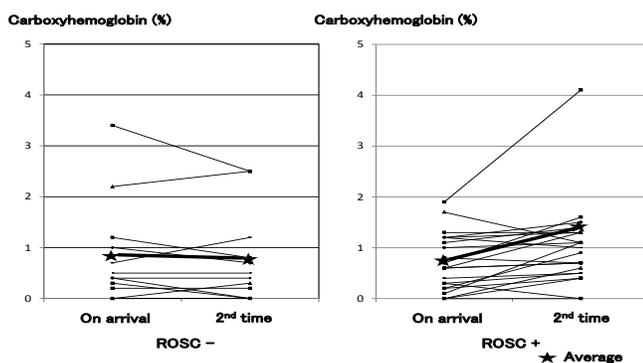


Figure 1. The time course of carboxyhemoglobin level changes.

The average 2nd level of carboxyhemoglobin tended to significantly increase in comparison with the 1st level in the ROSC+ group, while, the average 2nd level of carboxyhemoglobin tended to significantly decrease in comparison with the 1st level in the ROSC- group ($p < 0.05$). ROSC: return of spontaneous circulation; ROSC+, ROSC achieved; ROSC-, ROSC not achieved.

Discussion

In this report, we showed for the first time, the tendency for an association between carboxyhemoglobin level and ROSC; we also showed, through this prospective study, that the level of carboxyhemoglobin tended to increase after ROSC. The former finding, however, was not statistically significant ($p = 0.06$). The present report differed in several respects to the report by Yanagawa which demonstrated a statistically significant association between higher carboxyhemoglobin levels and survival in a comparison between surviving and non-surviving patients [6]. The average age of the patients in the present study was 71 years, while the average age in Yanagawa's study was 63 years. This investigation was performed in a rural district, while Yanagawa's was performed in an urban area. The society in Japan's rural areas is aging at a very high rate; [7] as a consequence, the average age of the patients in the present study was higher than that in Yanagawa's study. High age is associated with poor prognosis in patients with cardiopulmonary arrest [8,9]. The survival rate of this study (6/108=5.5%) was also smaller than that in Yanagawa's study (10.4%). Accordingly, the treatment of patients corresponding to poor prognostic groups might result in a failure to demonstrate statistical significance in regard to the level of carboxyhemoglobin. Furthermore, the investigation period might have been too short to collect samples that would be more likely to show a statistically significant difference.

In previous reports, biochemical-hematologic parameters such as base excess, lactate and ammonia have been shown to have a significant impact on outcome [10-13]. However, prehospital factors such as the frequency of witnessed collapse, bystander CPR and initial rhythm are known to be strong prognostic factors for cardiopulmonary arrest patients [14,15]. Few reports have investigated which of the prognostic factors (including prehospital prognostic factors and biochemical-hematologic parameters) is the most important [13]. Our results revealed that the level of carboxyhemoglobin, base excess, and lactate were weaker prognostic factors than ECG at the scene.

This study demonstrated that the level of carboxyhemoglobin tended to increase after ROSC. The level of carboxyhemoglobin changes under oxidative stress [16]. Godai et al. revealed that the level of carboxyhemoglobin is correlated with hepatic ischemia/reperfusion injury induced by inflow occlusion. Our patients with OH CPA underwent oxygen therapy under advanced cardiac life support. Ischemia/reperfusion injury also

occurs in patients with OH CPA who achieve ROSC [17,18]. As a result, the level of carboxyhemoglobin tended to increase when the OH CPA patients achieved ROSC.

Conclusion

There might be an association between carboxyhemoglobin level and ROSC, given that the level of carboxyhemoglobin tended to increase after ROSC. The Management of carboxyhemoglobin in patients with cardiopulmonary arrest might affect their prognosis.

Conflict of Interest

We had obtained Marumo Fund for Promotion of Research for Emergency Medicine concerning of this study.

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