CLINICAL STUDY

Neurological Prognostic Value of Adjusted Ca^{2+} Concentration in Adult Patients with Out-of-Hospital Cardiac Arrest

A Preliminary Observational Study

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Summary

Many patients are transferred to hospital due to out-of-hospital cardiac arrest (OHCA), and, unfortunately, most suffer from cerebral damage. Currently, it is difficult to predict the recovery of neurological function after return of spontaneous circulation (ROSC) in the acute phase. Increased intracellular Ca^{2+} induces cell death in the acute phase. Accordingly, we predicted that serum adjusted Ca^{2+} will decrease following Ca^{2+} influx into cells. Consequently, serum adjusted Ca^{2+} in the acute phase may be able to predict recovery of neurological function in patients with ROSC from OHCA. This is a retrospective and observational study from 2 centers. A total of 190 consecutive patients with ROSC from OHCA were recruited, with 33 patients meeting the inclusion criteria. The relationship between serum adjusted Ca^{2+} within 48 hours after ROSC and neurological function at discharge (as evaluated by the Glasgow-Pittsburgh cerebral performance category) was examined. Serum adjusted Ca^{2+} was measured every 4 hours within a 48-hour period after ROSC. There were no significant differences in hemodynamical state and laboratory data between the 2 groups. However, lowest serum adjusted Ca^{2+} within 48 hours after ROSC was significantly lower in the poor neurological outcome group (0.96 ± 0.06 versus 1.02 ± 0.06 mmol/L, $P = 0.011$). Thus, lowest serum adjusted Ca^{2+} within 48 hours after ROSC may be a predictive factor for recovery of neurological function at discharge in patients with ROSC from OHCA.

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Key words: Ionized calcium, Cerebral performance category, Return of spontaneous circulation

In Japan, around 120,000 people are transferred to hospital each year due to out-of-hospital cardiac arrest (OHCA).[1)] Although several treatments such as target temperature management (TTM) and extracorporeal membrane oxygenation (ECMO) have contributed to improved survival rates and attenuation of neurological damage,[2,3)] satisfactory outcomes have not been gained, and most patients with OHCA suffer from some damage in cerebral neurological function. A previous report from Japan showed that the proportion of individuals with cerebral performance categories (CPC) 1/2, 3/4, and 5 at 90 days after OHCA were 3.1%, 2.7%, and 90.9%, respectively.[4)] Although cerebral neurological outcome is helpful in anticipating the effect of treatment and providing the patient's family with information on their prognosis and planning their subsequent care, it is difficult to predict cerebral neurological function at the acute phase. A younger age, initial shockable rhythm (ventricular fibrillation and tachycardia), and time to return of spontaneous circulation (ROSC) are reported as predictive factors for a favorable neurological outcome in patients with OHCA.[5,6)] Serum ammonia on arrival at the emergency room is also recognized as a predictive factor.[7)] However, not all patients with these favorable factors achieve a favorable outcome. The limited relationship between these factors and neurological outcome may be partly explained by the fact that cerebral damage depends not only on pre-hospital but also on post-admission factors. Indeed, the N20 wave of somatosensory evoked potentials (SSEP) after admission is recognized as a predictor for adult comatose survivors of cardiac arrest.[8,9)] However, evaluation of N20 SSEP has limitations caused by sedation and noise, and it is difficult to perform in patients treated with TTM.[10)] Thus, there are difficulties in predicting the neurological function of patients with ROSC from OHCA in the acute phase. Nevertheless, predicting cerebral neurological outcome in the acute phase is useful in order to estimate the effect of treatment and consult the patient's family on their prognosis to support decision-making.

Intracellular calcium concentration rises in the brain during the ischemic and reperfusion phases and ultimately results in cell death through complex mechanisms such as

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generation of reactive oxygen species (ROS) and mitochondrial dysfunction.[11,12] In fact, a previous study reported that intracellular calcium concentration increases following severe sepsis in rats, which suggests that disruption of calcium homeostasis is related to poor clinical outcome in patients with severe septic shock.[13] Consequently, we hypothesized that serum ionized calcium (Ca^{2+}) concentration might be decreased by calcium influx into brain cells during the ischemic/reperfusion phases and that the amount of serum adjusted Ca^{2+} may reflect brain damage and predict neurological outcome in patients with ROSC from OHCA. Hence, this study aims to test our hypothesis that changes in serum Ca^{2+} concentration during the acute phase after admission have predictive value for neurological outcome at discharge in patients with ROSC from OHCA.

Methods

Consecutive adult patients with ROSC who were transferred to Tottori University Hospital between April 2013 and February 2017 or to Matsue Red Cross Hospital between January 2013 and April 2017 because of OHCA caused by cardiogenic reasons were retrospectively enrolled. Cardiogenic reasons included heart failure, acute coronary syndrome, and arrhythmia. The study subjects were unconscious (score ≤ 8 on the Glasgow Coma Scale) on admission after ROSC from OHCA. Patients were excluded if they were in good neurological condition (score > 9 on the Glasgow Coma Scale) after ROSC from OHCA in the emergency room, had a history of a malignant tumor, or had died before discharge. This study was approved by the Institutional Review Boards of Tottori University Hospital and Matsue Red Cross Hospital.

In patients treated with TTM, the target temperature was set according to 2 methods, as determined by the attending physician. The first stated that the temperature was maintained at 34°C for 24 hours after admission followed by rewarming by 0.5°C per hour, with maintenance at 36°C for 24 hours. The second stated retention of the temperature at 36°C for 72 hours after admission. During TTM therapy, patients were sedated with midazolam or dexmedetomidine. Muscle relaxants were also used to prevent heat production by shivering.

Assessment of serum Ca^{2+}: After admission in both hospitals, arterial blood gas data were routinely checked every 4 hours over the 48-hour period after admission. Since Ca^{2+} concentration adjusted by pH is considered the best indicator of physiological calcium activity, trends of adjusted Ca^{2+} were assessed as follows using blood gas data.

Adjusted Ca^{2+}: Adjusted Ca^{2+} = actual Ca^{2+} × (1 − 0.53 [7.4 − actual blood pH]).[14]

Since Ca^{2+} in severe acidosis or alkalosis (pH < 7.2 or > 7.7) is difficult to adjust in this formula, data < pH 7.2 or > pH 7.7 were excluded from the analysis. The relationship between lowest adjusted Ca^{2+} concentration during 48 hours after admission and neurological outcome at discharge was examined. Neurological outcomes were estimated before discharge using the Pittsburgh CPC.[15] CPC is a common evaluation method for the neurological outcome of patients with OHCA. CPC consists of 5 categories. Here, CPC 1 (good recovery) and CPC 2 (moderate disability) were defined as a favorable neurological outcome and CPC 3 (severe disability) and CPC4 (vegetative state) as an unfavorable neurological outcome.[16] Since CPC 5 indicates the state of death, patients at CPC 5 were excluded from the analysis. Neurological outcome was independently assessed from medical records by 3 doctors blinded to the serum adjusted Ca^{2+} data. Since CPC is a categorical variable, the majority decision on CPC assigned by the 3 investigators was used.

Statistical analysis: Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as percentages. To compare continuous variables between groups, *t*-tests were used. Chi-square tests were used to compare categorical variables. The threshold for significance was $P < 0.05$. All statistical analyses were performed using IBM SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 190 consecutive patients were admitted to hospital after ROSC from OHCA: 96 patients from Tottori University Hospital and 94 patients from Matsue Red Cross Hospital. Of these patients, we excluded 12 patients who showed good neurological function (score > 9 on the Glasgow Coma Scale at admission), 117 patients who died before discharge, 4 patients who had non-cardiac causes of OHCA, 10 patients who had insufficient follow-up data, 1 patient who had a malignant cancer history, and 13 patients who had poor activities of daily life (ADL) before admission. Therefore, only 33 patients were enrolled (Figure 1). Table I shows the characteristics of the patients. Among 33 patients, 22 had a favorable outcome (CPC 1 or 2) and 11 had an unfavorable outcome (CPC 3 or 4). Time from collapse to ROSC was shorter and the prevalence of shockable rhythm on the initial rhythm was higher in the favorable than in the unfavorable outcome group. The dose of epinephrine was lower in the favorable than in the unfavorable outcome group. There were no differences in the number of patients treated with ECMO, TTM, and percutaneous coronary intervention or with comorbidities between the 2 groups. In the clinical data (Table II), there were no significant differences in laboratory data or vital signs at admission between the 2 groups. The lowest value of adjusted Ca^{2+} during 48 hours after ROSC was significantly lower in the unfavorable than in the favorable outcome group ($P = 0.011$) (Figure 2). Figure 3 shows the receiver operating characteristic (ROC) curve of adjusted Ca^{2+} for detection of a favorable neurological outcome. The area under the ROC was 0.750.

Discussion

Among survivors of OHCA, the lowest value of adjusted Ca^{2+} during 48 hours after ROSC in patients with an unfavorable neurological outcome was significantly lower than those with a favorable neurological outcome, thereby supporting our hypothesis. There were no significant differences in clinical characteristics at admission be-

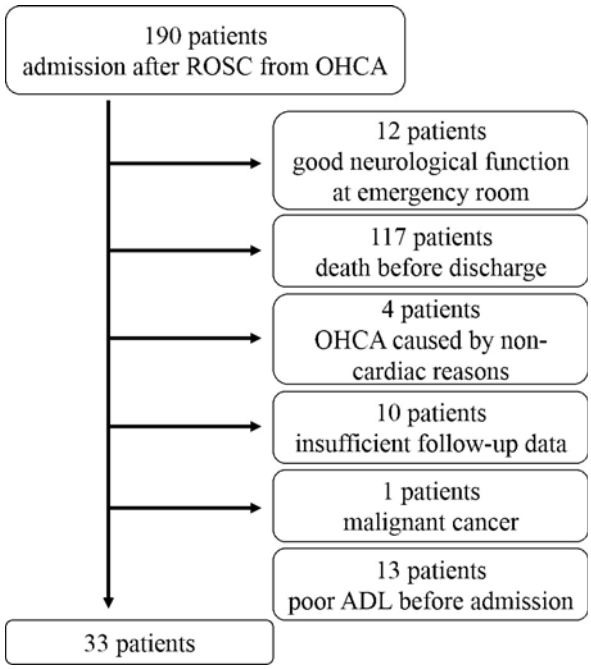

Figure 1. In this study, 190 consecutive patients with return of spontaneous circulation (ROSC) due to out-of-hospital cardiac arrest (OHCA) were enrolled. Subsequently, 157 patients were excluded due to the following reasons: good neurological findings in the emergency room, death before admission, non-cardiogenic OHCA, insufficient follow-up data, malignant cancer, or poor activities of daily living (ADL) before admission

tween the 2 groups, except for time from collapse to ROSC, prevalence of shockable rhythm on initial rhythm, and dose of epinephrine.

Ischemia and reperfusion injuries play important roles in cerebral damage in patients with ROSC from OHCA.[13] Ischemia induces anaerobic glycolytic metabolism, which leads to lactate formation and decreased ATP.[17] Acidification activates acid-sensing ion channels, while decreased ATP causes the failure of membrane pumps and the endoplasmic reticulum, both of which facilitate an influx of Ca^{2+},[18] leading to a 1000 to 10000-fold increase of intracellular Ca^{2+}.[19,20] During the reperfusion phase, restoration of blood flow causes the formation of ROS. Massive ROS generation induces a further increase of intracellular Ca^{2+} due to reticulum dysfunction and membrane pump failure, which accelerates cell death. Therefore, factors related to increasing intracellular Ca^{2+} are likely related to cerebral tissue damage and neurological outcome in survivors of OHCA. A previous report revealed a relationship between serum adjusted Ca^{2+} concentration and cerebral damage in newborns.[21] Accordingly, we hypothesized that adult patients with neurologically unfavorable outcomes after ROSC following OHCA would show a decrease of serum adjusted Ca^{2+} concentration through the increase of intracellular Ca^{2+}. A previous report revealed that neurological injury mainly occurs within 48 hours after ROSC.[22] Therefore, we analyzed data from admission to 48 hours after ROSC every 4 hours. Additional arterial blood gas was checked irregularly based on the decision of the consulting physician. The assessment of serum adjusted Ca^{2+} was performed 16.2 times on average per patient during 48 hours after

Table I. Characteristics of Patients

	Favorable outcome (n = 22)	Unfavorable outcome (n = 11)	P-value
Age (years)	57.2 ± 18.9	59.3 ± 14.5	0.75
Females	4 (18%)	0 (0%)	0.276
Witnessed arrest	16 (73%)	5 (45%)	0.149
Shockable rhythm	21 (95%)	7 (64%)	0.033
Bystander CPR	13 (59%)	3 (27%)	0.141
Defibrillation (times)	3.1 ± 2.9	6.0 ± 7.6	0.25
Epinephrine (mg)	1.1 ± 2.2	4.1 ± 3.0	0.002
ROSC time (minutes)	27.4 ± 20.0	64.3 ± 25.9	< 0.001
Length of stay in hospital (days)	40.2 ± 21.7	58.6 ± 29.7	0.052
TTM	18 (81%)	7 (63%)	0.391
ECMO	5 (23%)	6 (55%)	0.117
PCI	12 (55%)	4 (36%)	0.465
Comorbidity			
DM	2 (9%)	3 (27%)	0.304
HT	9 (41%)	2 (18%)	0.258
DL	4 (18%)	1 (9%)	0.643
HD	1 (5%)	1 (9%)	1
CHF	4 (18%)	2 (18%)	1
Smoking	13 (59%)	10 (90%)	0.109

Values represent mean ± SD or n (%). CHF indicates chronic heart failure; CPR, cardiopulmonary resuscitation; DL, dyslipidemia; DM, diabetic mellitus; ECMO, extracorporeal membrane oxygenation; HD, hemodialysis; HT, hypertension; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; and TTM, targeted temperature management.

Table II. Clinical Data of Patients

	Favorable outcome (n = 22)	Unfavorable outcome (n = 11)	P-value
On admission			
HR (bpm)	104.9 ± 32.1	102.8 ± 22.3	0.851
MBP (mmHg)	99.7 ± 27.7	106.4 ± 26.6	0.516
BT (°C)	35.0 ± 4.2	35.7 ± 0.5	0.614
WBC (10^3/μL)	11.2 ± 3.4	10.3 ± 2.6	0.413
PLT (10^3/μL)	210.8 ± 74.8	169.7 ± 62.1	0.127
Hb (g/dL)	13.8 ± 2.0	12.7 ± 2.3	0.17
CK (U/L)	417.5 ± 1287.4	205.3 ± 110.4	0.592
Peak CK (U/L)	3223.5 ± 3981.6	5998.2 ± 5797.0	0.116
CK-MB (ng/mL)	46.8 ± 30.5	49.5 ± 29.5	0.807
Peak CK-MB (ng/mL)	199.5 ± 271.0	331.1 ± 273.4	0.2
Cre (mg/dL)	1.6 ± 2.7	2.0 ± 2.6	0.67
NH_3 (μg/dL)	121.1 ± 142.7	168.1 ± 113.3	0.467
pH	7.3 ± 0.1	7.3 ± 0.1	0.156
pO_2 (mmHg)	165.8 ± 120.1	226.9 ± 140.7	0.202
Na (mmol/L)	138.2 ± 3.3	138.3 ± 5.1	0.951
Lactate (mmol/L)	7.9 ± 4.2	9.6 ± 4.6	0.293
Glucose (mg/dL)	250.5 ± 65.7	286.8 ± 87.4	0.19
At lowest adjusted Ca^{2+}			
pH	7.3 ± 0.1	7.3 ± 0.1	0.541
pO_2 (mmHg)	150.1 ± 77.5	210.5 ± 100	0.065
Na (mmol/L)	137.0 ± 3.4	137.7 ± 5.6	0.624
Lactate (mmol/L)	4.5 ± 2.5	5.1 ± 3.1	0.547
Glucose (mg/dL)	242.9 ± 78.1	209.2 ± 44.2	0.124

Values represent mean ± SD. BT indicates body temperature; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; Cre, creatine; Hb, hemoglobin; HR, heart rate; MBP, mean blood pressure; Na, sodium; NH_3, ammonia; PLT, platelet; pO_2, partial pressure of oxygen; and WBC, white blood cell.

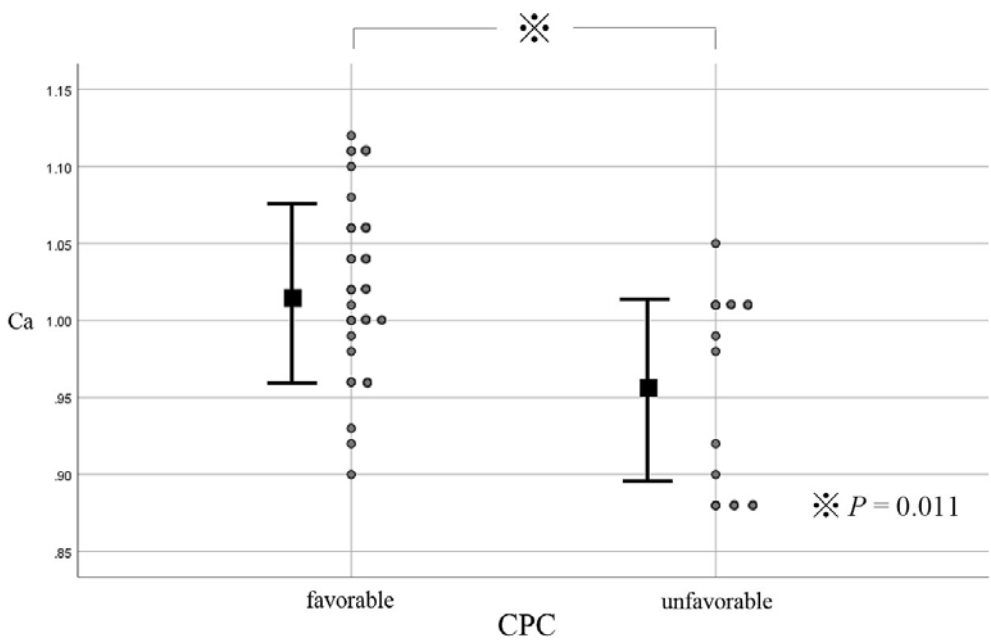

Figure 2. The relationship between lowest serum adjusted Ca^{2+} and neurological outcome. Lowest serum adjusted Ca^{2+} was lower in the unfavorable than in the favorable outcome group (0.96 ± 0.06 versus 1.02 ± 0.06 mmol/L, P = 0.011). Each dot represents a serum adjusted Ca^{2+} value for a patient. Solid squares indicate the mean value of each group, and vertical bars indicate ± SD. CPC indicates cerebral performance category

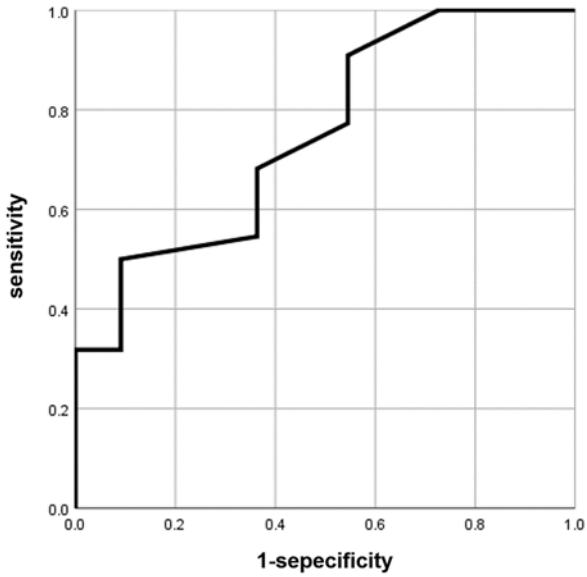

Figure 3. Receiver operating characteristic analysis for the prediction of favorable neurological outcome. The area under the receiver operating characteristic (ROC) curve was 0.750

ROSC. The results of our current study support our hypothesis that serum adjusted Ca^{2+} concentration predicts neurological outcome in survivors of OHCA. Although restoration of blood flow after ischemia is essential to salvage cerebral tissue, reperfusion also accelerates cerebral damage through the generation of ROS. One of the causes for ROS overproduction during reperfusion is hyperoxia.[23] In this study, partial pressure of oxygen was not significantly different between the 2 groups at admission or at the time of the lowest value of adjusted Ca^{2+} during 48 hours after ROSC. Thus, differences in oxygenation after reperfusion may not be responsible for the different neurological outcomes between the groups in this study.

Both mortality and neurological outcome involve similar factors but, nonetheless, are unlikely to be affected by identical factors. A previous study showed that serum Ca^{2+} concentration decreased in patients with a severe sepsis condition due to microcirculatory dysfunction.[24] Therefore, serum adjusted Ca^{2+} concentration in patients after ROSC may not reflect cerebral damage only, and future studies are necessary to clarify the cause of the decrease in serum adjusted Ca^{2+} concentration in patients with unfavorable neurological outcomes after ROSC.

This study shows a relationship between the lowest value of serum adjusted Ca^{2+} concentration within 48 hours after ROSC and neurological outcome at discharge. However, using the best cutoff value of adjusted Ca^{2+} (1.015 mmol/L) on the ROC curve for prediction of a favorable neurological outcome (Figure 3), the sensitivity was 0.50 and specificity was 0.91, while the positive predictive value was 0.92 and negative predictive value was 0.48. Thus, although patients with the lowest serum adjusted Ca^{2+} (> 1.015 mmol/L) are expected to have a favorable neurological outcome, the neurological outcome of patients with lowest serum adjusted Ca^{2+} (< 1.015 mmol/L) should not be decided at the acute phase due to its low negative predictive value. Thus, our findings do not immediately affect the current treatment strategy of patients with OHCA, but may contribute to future improvement of the treatment strategy by highlighting the close relationship between serum Ca^{2+} and neurological outcome.

Our study has several limitations. First, this study was retrospective and included a small number of patients. Second, the neurological outcomes of patients were assessed at discharge, yet the duration of hospital stays was different among patients. In addition, neurological status can change after discharge. Therefore, the results of our study are limited to prediction of short-term neurological outcome after ROSC. Third, evaluation of adjusted Ca^{2+} could not be performed continuously; therefore, we were unable to estimate the lowest value of adjusted Ca^{2+} concentration in all of the patients.

Conclusion

We found that the lowest value of adjusted Ca^{2+} concentration within 48 hours after ROSC was lower in patients with OHCA and an unfavorable neurological outcome at discharge than those with a favorable outcome. Lowest serum adjusted Ca^{2+} concentration may predict short-term neurological outcome after ROSC in patients with OHCA. Future studies with a larger number of patients are necessary to confirm these findings.

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Disclosure

Conflicts of interest: The authors declare that they have no conflicts of interest.

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