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Selected Topics: Critical Care

BLOOD pH IS A USEFUL INDICATOR FOR INITIATION OF THERAPEUTIC HYPOTHERMIA IN THE EARLY PHASE OF RESUSCITATION AFTER COMATOSE CARDIAC ARREST: A RETROSPECTIVE STUDY

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☐ **Abstract—Background: Therapeutic hypothermia (TH) is one of the key treatments after cardiac arrest (CA). Selection of post-CA patients for TH remains problematic, as there are no clinically validated tools to determine who might benefit from the therapy. Objective: The aim of this study was to investigate retrospectively whether laboratory findings or other patient data obtained during the early phase of hospital admission could be correlated with neurological outcome after TH in comatose survivors of CA. Methods: Medical charts of witnessed CA patients admitted between June 2003 and July 2009 who were treated with TH were reviewed retrospectively. The subjects were grouped based on their cerebral performance category (CPC) 6 months after CA, as either good recovery (GR) for CPC 1–2 or non-good recovery (non-GR) for CPC 3–5. The following well-known determinants of outcome obtained during the early phase of hospital admission were evaluated: age, gender, body mass index, cardiac origin, presence of ventricular fibrillation (VF), time from collapse to cardiopulmonary resuscitation, time from collapse to return of spontaneous circulation, body temperature, arterial blood gases, and blood test results. Results: We analyzed a total of 50 (25 GR and 25 non-GR) patients. Multivariate logistic analysis showed that initial heart rhythm and pH levels were significantly higher in the GR group than in the non-GR group (ventricular tachycardia/VF rate: $p = 0.055$, 95% confidence interval [CI] 0.768–84.272, odds ratio [OR] 8.047; pH: 7.155 ± 0.139 vs. 6.895 ± 0.100, respectively, $p < 0.001$, 95% CI 1.838–25.827; OR 6.89). Conclusion: These results imply that in addition to initial heart rhythm, pH level may be a good candidate for neurological outcome predictor even though previous research has found no correlation between initial pH value and neurological outcome. Crown Copyright © 2013 Published by Elsevier Inc.**

☐ **Keywords—cardiopulmonary resuscitation; therapeutic hypothermia; pH; outcome predictor**

INTRODUCTION

Therapeutic hypothermia (TH) improves the probability of both survival and neurologic recovery after resuscitation from cardiac arrest (CA), even in patients who are predicted to have a poor outcome based upon neurological examination or electroencephalogram (EEG) (1–5). However, not all comatose survivors of CA are able to regain consciousness after TH (favorable outcome is 75/136 (52.9%) and 21/43 (48.8%), respectively) (1,2,6). Selection of post-CA patients for TH remains problematic, as there are no clinically validated tools to determine who might benefit from the therapy (7,8).

To date, initial heart rhythm, time from collapse to return of spontaneous circulation (ROSC), pH, partial pressure of carbon dioxide (pCO_2), partial pressure of

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oxygen (pO_2), base excess (BE) of arterial blood gas analysis (BGA), and blood hemoglobin level on arrival at the hospital have been reported to correlate with the neurological prognosis of post-CA patients (4,8–10). Moreover, EEGs, including the bispectral index and pupillary reaction to light or corneal reflex during the TH period, are beneficial for neurological prognostication of post-CA patients (11,12). It may be that several predictor candidates of laboratory data and EEG changes during TH might not be useful as predictors of good neurological outcomes in CA patients before starting TH, because atypical laboratory examinations and changes on electrocardiogram would take time to get the results (5,13–16). Additionally, a recent case report claimed that a favorable outcome might be possible even in patients with initially poor prognostic signs (17,18).

In this study, we performed a retrospective chart review to find out which laboratory findings or other patient data evaluated at the time of arrival to the hospital might be associated with neurological outcome in CA patients treated with TH.

METHODS

Patients

We conducted a retrospective cohort study of consecutive non-traumatic CA patients in whom ROSC was accomplished either in or out of the hospital, after admission to the intensive care unit of the Critical Care and Emergency Centre, Yokohama City University Medical Center, from June 2003 to July 2009. All patients were Japanese. Because no study intervention was performed and due to the retrospective design, the ethical review board of Yokohama City University Medical Center waived the need for informed consent.

Patient Care and Therapeutic Hypothermia

For all patients, basic and advanced life support, as well as post-resuscitation care, were performed by an emergency physician at the scene or at the Emergency Department (ED) according to standard protocols. We performed TH for CA patients fulfilling the following criteria: ROSC, < 75 years of age, <90 mm Hg blood pressure with continuous epinephrine infusion <0.2 mcg/kg/min, satisfactory level of daily activity before CA (not bedridden status or severe dementia), Glasgow Coma Scale score of ≤6, and normal brain computed tomography scan. In contrast, TH was not used in patients if any of the following conditions existed: trauma, severe bleeding, terminal stage of chronic disease, when no further intensive care was appropriate, pregnancy, severe coagulopathy, or chronic liver disease. Patients selected for TH were cooled to a target core temperature of 34°C using an infusion of chilled (approx. 4°C) fluids and a commercially available cooling system with external pads (Blanketrol® II, Cincinnati Sub-Zero Products, Inc., Cincinnati, OH, or Arctic Sun® 2000, Medivance, Inc., Louisville, CO). The target temperature was maintained for 24 h via external pads and an indwelling bladder-temperature monitoring system. All patients were administered midazolam or propofol as a sedative and rocuronium for neuromuscular blockade. After completion of the 24-h TH maintenance period, rewarming to 36°C and discontinuation of rocuronium were performed.

A patient was included in the study by meeting the additional following four criteria: 1) those whose cardiac arrest was witnessed; 2) those who underwent therapeutic hypothermia after cardiac arrest; 3) those with blood samples for BGA analysis and blood testing obtained within 30 min of arrival at the hospital; and 4) those with complete data sets for analysis.

Outcome Definition

Utstein definitions were used to register the data. We rated the patients based on the Glasgow-Pittsburgh cerebral performance category (GP-CPC) scale 6 months after CA, as follows: GP-CPC 1, good cerebral performance; GP-CPC 2, moderate cerebral disability; GP-CPC 3, severe cerebral disability; GP-CPC 4, coma or vegetative state; and GP-CPC 5, death (19). Patients who survived up to 6 months with good neurological status (i.e., GP-CPC 1–2) were classified into the "good recovery" (GR) group, and those with GP-CPC 3–5 were classified into the "non-good recovery" (non-GR) group. Cerebral performance was evaluated by neurologists at our hospital and GP-CPC scores were estimated from medical charts.

Data Analyses and Statistical Methods

Individual medical records were reviewed for the following data: age, gender, body mass index (BMI), electrocardiogram (ECG) rhythm at the scene (whether or not ventricular fibrillation [VF] was noted), cause of cardiac arrest, time from collapse to cardiopulmonary resuscitation (CPR), time from collapse to ROSC, core temperature on admission, BGA data, including hemoglobin, glucose, lactate, BE, pCO_2, and pH values obtained within 30 min of the patient's arrival at the hospital.

Univariate analyses for comparisons between the GR and non-GR groups were performed using either the two-tailed Student's *t*-test or the Fisher's exact test. Adjusted odds ratios were calculated using multiple logistic regression analysis to determine the clinical factors significantly associated with neurological outcomes.

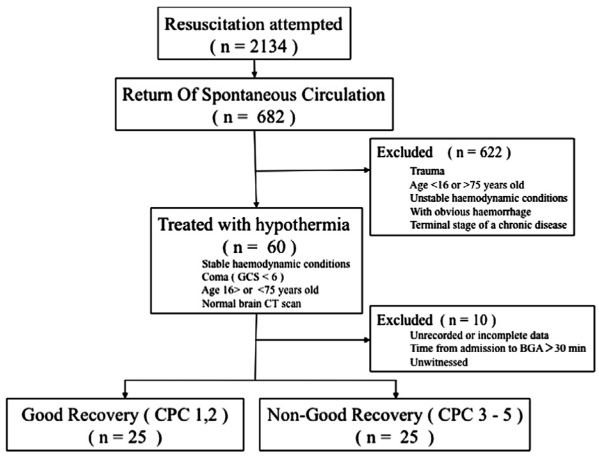

Figure 1. Flow chart of our retrospective study showing inclusion and exclusion criteria. GCS = Glasgow Coma Scale score; CT = computed tomography; BGA = blood gas analysis; CPC = cerebral performance category.

All statistical analyses were performed using Microsoft Excel 2011 for Macintosh (Microsoft, Redmond, WA) with a statistical macro (XLSTAT; Addinsoft, New York, NY). We considered $p < 0.01$ to be statistically significant due to the small sample size of this study.

RESULTS

Study Population

During the time period of the study, 682 (31.9%) post-CA patients achieved ROSC among 2134 patients who were admitted to our center after resuscitation for CA. Of those, 60 were treated with TH according to the hospital's post-arrest/TH protocol. Among the patients who underwent TH, 10 were excluded from this study due to incomplete data or lack of witness at the scene. Thus, 50 (2.3%) patients were deemed eligible for the present study and were enrolled in the study. Of the 50 patients, 25 (50%) were classified into the GR group (survival > 6 months with GP-CPC 1–2) and 25 (50%) were included in the non-GR group (survival > 6 months with GP-CPC 3–5) (Figure 1). The demographic data and other basic data regarding CA and emergency medical care in study patients are presented in Table 1.

Univariate Analysis of Demographic Data and BGA Results

Univariate analysis of demographic data and BGA values are also shown in Table 1. No significant differences between the GR and non-GR groups were evident in terms of age, gender, time from collapse to CPR, time from collapse to ROSC, temperature, time from arrival to BGA analysis, or blood glucose levels. As compared to the GR group, the non-GR group displayed a higher BMI, lower VF-ventricular tachycardia (VT) rate in initial heart rhythm, lower blood hemoglobin level, lower mean pH, higher pCO_2, higher mean lactate level, and higher mean BE, all with statistical significance.

Table 1. Demographic Data in Total Population, GR Group, and Non-GR Group upon Arrival at Emergency Department

	GR (n = 25)	Non-GR (n = 25)	*p*-Value
Age (years)	57 [18–72]	61 [17–76]	0.903
Gender (male)	20 (80%)	21 (84%)	0.803
BMI	22.7 [14.7–26.9]	23.8 [14.9–29.4]	0.049*
Presumed cause of arrest			0.221
Cardiac	24 (96%)	20 (80%)	
Hypoxia	1 (4%)	3 (12%)	
Overdose	0 (0%)	2 (8%)	
Initial rhythm			0.020†
VF-VT	20 (80%)	11 (44%)	
Non-VF-VT	5 (20%)	14 (56%)	
Time from collapse to CPR (min)	5 [0–11]	5 [0–20]	0.062
Time from collapse to ROSC (min)	22 [3–111]	31 [3–130]	0.388
Temperature on admission (°C)	36.3 [34.5–37.4]	36.2 [34.0–40.1]	0.964
Time from arrival to BGA (min)	12 [2–30]	10 [6–30]	0.65
Hemoglobin (g/dL)	14.3 [11.6–20.8]	13.7 [7.9–17.3]	0.024*
Glucose (mg/dL)	265 [107–441]	284 [106–617]	0.314
Lactate (mmol/L)	8.7 [3.2–17.2]	11.4 [5.8–21.9]	0.019*
Base excess (mmol/L)	−12.3 [−25.5–−5.6]	−17.8 [−25–−8.6]	<0.01*
pCO_2 (mm Hg)	40.8 [26.4–96.3]	79.3 [47.7–140.5]	<0.01*
pH	7.17 [6.894–7.4]	6.866 [6.666–7.092]	<0.01*

GR = good recovery; BMI = body mass index; VF-VT = ventricular fibrillation-ventricular tachycardia; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation; BGA = arterial blood gases.
Data were presented as mean [range] or number of patients [percentage of group total].
* Compared with Student's *t*-test.
† Compared with Fisher's exact test.

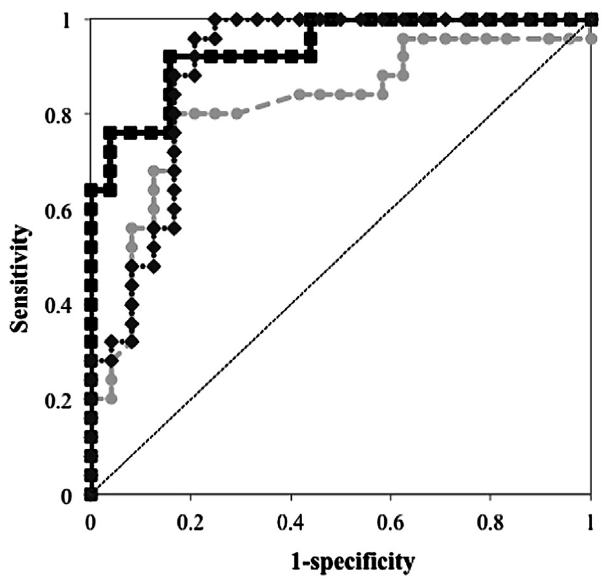

Figure 2. Receiver-operator characteristic (ROC) curves for pH, partial pressure of carbon dioxide (pCO$_2$), and base excess (BE) of arterial blood gas analysis. The areas under the curve were 0.934 (95% confidence interval [CI] 0.887–0.982; black-filled square) for pH, 0.895 (95% CI 0.809–0.981; gray-filled diamond) for pCO$_2$, and 0.812 (95% CI 0.692–0.931; pale-filled circle) for BE.

Correlations between pCO$_2$, BE, Lactate, and pH

In performing multivariate logistic regression analyses on our data, we considered and attempted to avoid multi-colinearity among predictor variables (20). The blood pH determined by pCO$_2$, BE, and HCO_3^- is precisely linked to serum lactate, which reflects tissue hypoperfusion (21,22).

The extent of colinearity between the seven variables, determined to be statistically significant in the comparison between the GR and non-GR groups, was calculated and referred to as the variance inflation factor (VIF) because a VIF of >10 is suggested to be of concern (23). Among those seven variables, we found that pH, pCO$_2$, and BE in BGA had VIFs of >10 (pH: 29.6, pCO$_2$: 11.7, BE: 10.4), and we needed to select one variable for multivariate logistic analysis from among pH, pCO$_2$, and BE. We performed linear regression analysis between pH and pCO$_2$, BE, and lactate, which were considered as determinants of arterial blood pH. As expected, pCO$_2$, BE, and lactate had a significant correlation with arterial blood pH (pH and pCO$_2$: $r = 0.812$, $p < 0.001$, pH and BE: $r = 0.785$, $p < 0.001$). Receiver operating characteristic (ROC) curves for pH, pCO$_2$, and BE indicated that pH was the most efficient predictor for good recovery of neurological outcome (Figure 2, Table 2); therefore, we opted to use pH from among these variables for multivariate logistic regression analysis.

Table 2. AUC, Cutoff Value of Each Predictor and its Sensitivity/Specificity

	AUC (95% CI)	Cutoff Value	Sensitivity	Specificity
pH	0.934 (0.887–0.982)	6.968	0.92	0.84
pCO$_2$	0.895 (0.801–0.981)	58.1 (toll)	0.88	0.833
Base excess	0.812 (0.692–0.931)	−16.4 (mmol)	0.8	0.833

AUC = area under the curve; CI = confidence interval.

Multivariate Logistic Regression Analysis

The results of the multivariate logistic regression analysis were used to evaluate the independent factors of initial heart rhythm, BMI, hemoglobin content, lactate, and pH for predicting good recovery of neurological outcome. A significant correlation was observed for VT/VF rate and pH (adjusted odds ratio [degrees of freedom, 0.1], VT/VF rate: 8.047, pH: 6.890, 95% confidence interval, VT/VF rate: 0.768–84.272, pH: 1.838–25.827, respectively), that is, in addition to initial heart rhythm, the pH value was also independently associated with a good neurological outcome (Table 3).

DISCUSSION

This retrospective study demonstrates that post-CA patients with a favorable outcome tended to have a higher VT/VF rate of initial rhythm, higher hemoglobin, BE, and pH values and lower BMI, lactate, and pCO$_2$ values compared to those with a poor outcome. Upon comparing ROC curves, pH was shown to be the most valuable predictor, among pH, pCO$_2$, and BE, which were mutually correlated for association of neurological outcomes of post-CA patients who received TH. Moreover, multivariate analysis revealed that pH was independently associated with a favorable neurological outcome, rather than initial heart rhythm.

Sudden CA survivors suffer from an ischemic brain injury that may lead to poor neurological outcomes and death (24). Reperfusion brain injury is associated with damaging biochemical reactions, which are suppressed

Table 3. Multivariate Logistic Regression Analysis of Prognostic Factors for Survival

Prognostic Factors	Adjusted Odds Ratio	95% Confidence Interval	p-Value
Initial VF	8.047	0.768–84.272	0.055
BMI	0.782	0.531–1.152	0.189
Hemoglobin	1.186	0.597–2.353	0.623
Lactate	1.016	0.731–1.401	0.923
pH	6.89	1.838–25.827	<0.001

VF = ventricular fibrillation; BMI = body mass index.

by TH (25). To date, TH is the only treatment shown to improve both survival and neurological outcomes in comatose survivors of CA (1,2). The 2005 CPR Guidelines and 2008 International Liaison Committee on Resuscitation consensus statement recommended that unconscious adult patients with ROSC after out-of-hospital CA should be cooled to 32–34°C for 12–24 h when the initial rhythm has been established as VF (26,27). The 2010 Cardiopulmonary Resuscitation Guidelines included post-CA care (27,28). Although it has been proven beneficial only for comatose patients with initial VF, the Scandinavian Society of Anesthesiology and Intensive Care Medicine Task Force on Therapeutic Hypothermia recommended TH after ROSC—if active treatment is decided—in comatose patients with initial pulseless electrical activity and asystole (29).

In this study, we were able to identify several variables that have significant association with favorable outcomes from data obtained at the early phase of patients' arrival at the hospital. Conventional bystander CPR, positive papillary reflex, and spontaneous respiration upon arrival in the ED, as well as a cardiac cause for the initial arrest, are predictors for GP-CPC class 1 outcome among adult patients with out-of-hospital CA (30). In the present study, however, most patients were unconscious on arrival, and the initial ECG rhythm was not always VF. The induction of TH is known to be associated with a significant improvement in neurological outcome in patients whose initial ECG rhythm is VF, but not in patients with other rhythms (31). Recent animal studies demonstrated that the induction of hypothermia during CA (intra-arrest cooling) enhances neurological benefits; the sooner the cooling is initiated in CA, the better the outcome (32–34). In clinical studies, early attainment of a lower core temperature has been proven to correlate with neurological benefits for patients with out-of-hospital CA who undergo cardiopulmonary bypass and percutaneous coronary intervention (35). Identifying neurological prognostic factors in patients with CA as early and accurately as possible is critical to determining therapeutic strategies after successful CPR, and to avoiding medical futility (36). In patients in whom the indications for TH are controversial, it would be ideal to decide for or against TH induction in the early phase of the patient's arrival at the hospital.

Moreover, recent studies have reported favorable outcomes even in patients with initial poor prognostic signs (17,18). It should be noted that clinical prognostication in the first 2–3 days after CA is difficult (37,38). A multi-center prospective study involving blood sampling post-resuscitation at a specified time point after the onset of CA would be most helpful in investigating the clinical usefulness of S-100 calcium binding protein B and neuron-specific enolase as early predictors of neurological outcomes (39). However, despite their usefulness, these factors could not be utilized in all hospitals or be evaluated in the early phase of patient arrival.

Our multivariate analysis indicated that a higher pH value was associated with favorable outcomes in patients who had undergone TH regardless of the initial rhythm, even though previous research concluded that there was no correlation between initial pH value and neurological outcome in in-hospital CA patients (40). Hence, our findings could be helpful when deciding upon TH for CA patients as soon as they are brought to the ED, even if they were previously thought to have a poor prognosis.

A longer estimated duration of CA is associated with a poor rather than a favorable outcome. Accordingly, lower values of pO_2 and higher values of pCO_2 and potassium have been observed in poor-outcome patients when compared to favorable-outcome patients (41). However, our study showed that BGA pH could be an independent predictor of survival after ROSC. This result could be explained by the following mechanisms: CA and the consequent interruption of blood flow to metabolically active tissues cause intense hypercarbia and metabolic acidosis at the tissue level (42). These abnormalities are the result of a shift from aerobic to anaerobic metabolism as well as the accumulation of end products, such as CO_2, lactate, and hydrogen ions. Even when conventional closed-chest resuscitation is applied, the systemic and regional blood flow generated rarely exceeds one quarter of the normal, thus failing to fully meet tissue metabolic demands (43,44). As a result, tissue acidosis would persist during the conventional resuscitation period and early post-arrest stage even after ROSC (45). Metabolic acidosis, ventilation status, and lung perfusion during CPR and ROSC periods affect pH and pCO_2 levels.

Limitations

Our study had numerous limitations, not the least of which is due to the inherent characteristics of its retrospective design. The number of patients who met the inclusion criteria may constitute a sample that was too small for an accurate interpretation of the results. Furthermore, this study was performed at a single, academic medical center with dedicated research and clinical staff to assist in the identification, enrollment, and management of patients eligible for TH; therefore, these results may not be generalizable to other institutions with different inclusion and exclusion criteria for TH. Moreover, it should be pointed out that BGA results might be difficult to distinguish from venous blood before ROSC; so, blood pO_2 might not correlate with neurological outcomes, whereas a previous study indicated that pO_2 was one of the predictors of neurological outcome

(9). Furthermore, the time at which BGA values were obtained could differ for patients even though they were obtained within 30 min in all cases in this study. BGA analyses were performed either before or after ROSC, and ventilation after ROSC is known to affect pCO_2 and pH values, which may have affected the results. Further prospective clinical studies are needed to clarify the value of BGA pH as a prognosticator of favorable neurological outcomes in CA patients.

CONCLUSION

In our study, arterial blood pH values in the early timing of hospital admission differed markedly between the GR and non-GR groups. This difference was an independent predictor of mortality in resuscitated CA patients. These results imply that in addition to initial heart rhythm, pH level is thought to be a candidate for good neurological outcome predictor. Future studies should be conducted to confirm these results with modifications to address an adequate sampling time, earlier induction, and wider indications.

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ARTICLE SUMMARY

1. Why is this topic important?

Despite the fact that therapeutic hypothermia has been widely implemented, it has been inconsistently applied. The initial examination obtained in the Emergency Department may affect the indication for therapeutic hypothermia in a patient for whom aggressive treatment after recovery from unwitnessed cardiac arrest is controversial.

2. What does this study attempt to show?

We attempted to find independent predictor of neurological outcome after return of spontaneous circulation. Independent predictor which were taken at early phase of resuscitation might be useful for indication of therapeutic hypothermia.

3. What are the key findings?

pH level is thought to be a candidate for good neurological outcome predictor, compared with other factors. The homeostatic balance of the patient is the most important factor during the early phase of resuscitation, after return of spontaneous circulation.

4. How is patient care impacted?

Therapeutic hypothermia may be more widely applied using a simple indication such as pH level.