Available online at www.sciencedirect.com

Resuscitation Plus

journal homepage: www.elsevier.com/locate/resuscitation-plus

Clinical paper

Dynamic changes of the hemoglobin index during resuscitation in patients with out-of-hospital cardiopulmonary arrest due to freshwater drowning: A retrospective observational study

Tomoya Hirose [a,*], Tomohiko Sakai [a], Ryosuke Takegawa [a], Mitsuo Ohnishi [b], Jotaro Tachino [a], Arisa Muratsu [a], Shunichiro Nakao [a], Tadahiko Shiozaki [a]

[a] Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, 2-15 Yamadaoka, Suita, Osaka 565-0871, Japan

[b] Traumatology and Critical Care Medical Center, National Hospital Organization Osaka National Hospital, 2-1-14 Hoenzaka, Chuo-Ku, Osaka-city, Osaka 540-0006, Japan

Abstract

Background: The hemoglobin index (HbI) represents the amount of hemoglobin, which reflects the regional tissue blood volume. The HbI is calculated by a regional oxygen saturation monitor. In freshwater drowning, inhaled water is immediately absorbed into the blood causing hemodilution. We hypothesized that this blood dilution could be observed in real time using HbI values in patients with out-of-hospital cardiac arrest (OHCA) due to freshwater drowning.

Methods: In this single-center retrospective, observational study, we examined the HbI in patients with OHCA due to freshwater drowning from April 2015 to May 2020. Patients with OHCA due to hanging were selected as a control group.

Results: Thirty-two patients in the freshwater drowning group and 21 in the control group were eligible for inclusion. In the freshwater drowning group, the HbI values in the return of spontaneous circulation (ROSC) group were significantly decreased in comparison to the non-ROSC group (−0.28 [IQR −0.55, −0.12] vs. −0.04 [IQR −0.16, 0.025]; p = 0.024). In the control group, the change of HbI during resuscitation in the ROSC and non-ROSC groups was not significantly dierent (0.11 [IQR −0.3525, 0.4225] vs. −0.02 [IQR −0.14, 0.605]; p = 0.8228). In each patient with ROSC in the freshwater drowning group, the HbI value after ROSC was significantly decreased in comparison to before ROSC (1.2±0.5 vs. 0.9 ±0.5]; p = 0.0156). In contrast, this dierence was not observed in patients with an ROSC in the control group (3.7±1.3 vs. 3.8±1.4]; p = 0.7940).

Conclusion: Blood dilution induced by freshwater drowning might be detected in real time using the HbI. To prove the validity of this research's result, further prospective large study is needed.

Keywords: Near-infrared spectroscopy, Regional oxygen saturation (rSO_2), Return of spontaneous circulation (ROSC), Blood dilution, Aspiration

Introduction

In recent years, measurement of cerebral regional oxygen saturation (rSO_2) by near-infrared spectroscopy (NIRS) has been studied in the resuscitation field [1]. Our group has reported the effect of cerebral rSO_2 monitoring during resuscitation in patients with out-of-hospital cardiac arrest (OHCA) for several years [2–7]. In addition to cerebral rSO_2, we have also recorded the hemoglobin index (HbI) [8]. The HbI is the amount of hemoglobin measured by near-infrared radiation and is determined by the measurement of light intensity received at 805 nm. It is also correlated with the regional blood volume. Myers et al. reported that the tissue HbI was correlated with the total hemo-

* Corresponding author.
E-mail address: htomoya1979@hp-emerg.med.osaka-u.ac.jp (T. Hirose).

https://doi.org/10.1016/j.resplu.2021.100179
Received 16 July 2021; Received in revised form 13 October 2021; Accepted 19 October 2021
Available online xxxx

globin concentration (Hbt), with Hbt ranging from 14 to 4 g/dl in an animal model [9].

During our studies, we noticed a decrease in HbI values after a return of spontaneous circulation (ROSC) in patients with cardiopulmonary arrest (CPA) due to freshwater drowning. Previously, in freshwater aspiration, hypotonic fluid passes through the lung into the pulmonary and systemic vasculature, causing hemodilution [10,11]. The blood volume increases within 3 to 4 minutes after aspiration, and the concentrations of most serum electrolytes decrease [11]. But, recently, the homodilution itself was doubtful, because the volume of water aspirated was reported to be very low, though the exact amount unknown [12,13]. However, in this time, we hypothesized that we could observe this blood dilution induced by freshwater drowning in real time as a decrease in HbI values. To our knowledge, no previous studies have reported the detection of hemodilution caused by freshwater drowning in real time. It may also provide new insights into the pathology of drowning. Thus, in this study, we retrospectively examined the changes in the HbI values of patients with OHCA due to freshwater drowning.

Methods

Study design, population, and setting

This was a retrospective observational study that was approved by the Ethics Committee of Osaka University Graduate School of Medicine (No. 20516-2). The subjects were all patients with CPA who were transferred to Osaka University Graduate School of Medicine (Osaka, Japan) form April 2015 to May 2020. The local institutional review board waived the requirement for informed consent because all subjects were in CPA.

We included patients with OHCA due to freshwater drowning. In this study, freshwater drowning was defined by the patient being found with their face completely submerged. As a control group, we selected patients with OHCA due to hanging because these patients did not inhale freshwater into their lungs. We excluded the following patients: those with i) missing data (rSO_2 and HbI); and ii) patients with ROSC in the prehospital setting because we could not evaluate the changes of rSO_2 and HbI before and after ROSC.

The sensor of the rSO_2 monitor (described below) was attached to the patient's forehead in the emergency department. During resuscitation, the medical staff could see the rSO_2 and HbI values, which were automatically recorded, displayed on the monitor. However, the treatment was not changed according to the cerebral rSO_2 and HbI data. We retrospectively collected and analyzed the data from these patients with CPA.

NIRS rSO_2 and HbI monitoring system

An rSO_2 monitor (TOS-OR; TOS-TEC., Tokyo, Japan) [6,8,14] was used to measure the cerebral rSO_2 and HbI values. The TOS-OR system measures the oxygen saturation based on the Beer–Lambert law, using three different wavelengths of near-infrared LED light, with absorbance specific to oxyhemoglobin and deoxyhemoglobin. The lights pass through the skin to a depth of approximately 3 cm, and the reflected light is sensed by a photodiode. The reflected light mainly represents the hemoglobin information in the cerebral cortex. The system can measure rSO_2 data every second without the need for cardiac pulsation.

The HbI represents the amount of hemoglobin that is present just beneath the sensor [8,14]. This does not reflect the local hemoglobin concentration around the brain cortex. The HbI is the relative value of an abstract number and thus has no units. We assumed a phantom standard of 1. The TOS can compare HbI values between patients using a phantom.

In the TOS, a calculation method that uses a combination of a calibration curve and phantom (calibrator) is adopted based on the abovementioned facts. This results in a system with reliably reproducible values and also enables correction of variation in the elements of the sensor. We assumed a phantom standard of 1. The TOS can compare HbI values between patients using a phantom.

Evaluation of serial changes of rSO_2 and HbI

The system can measure rSO_2 and HbI data every second without the need for arterial pulsation. It is therefore possible to perform continuous monitoring in CPA patients. Two rSO_2 and HbI values, one from the left side and one from the right side, are acquired continuously, and then the average of the two values is calculated.

Endpoint

The primary outcome was the change of HbI values during resuscitation between the ROSC and non- ROSC groups in patients with OHCA due to freshwater drowning or hanging (as a control group). The secondary outcome was the changes of HbI values in each patient with OHCA due to freshwater drowning or hanging (as control). In the ROSC group, we evaluated the HbI values before and after ROSC. In the non-ROSC group, we evaluated the initial HbI value and the terminal HbI values during resuscitation.

Statistical analysis

Patient characteristics and outcomes were compared between two groups using the Wilcoxon signed-rank test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. The Wilcoxon rank sum test was used to compare the differences between before and after ROSC in each patient. Data are summarized using the median and interquartile range (IQR) for continuous variables and as the frequencies and percentages for categorical variables. P values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with JMP Pro 13 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Fig. 1 shows the patient flow in the present study. During the study period, 771 patients with OHCA were transferred to our hospital. Among them, 51 cases were due to freshwater drowning. We excluded patients for the following reasons: (i) failure to measure rSO_2 and HbI (n = 15); and (ii) ROSC in the prehospital setting (n = 1). Finally, 32 patients were eligible for our analysis. In the control group, 32 patients experienced OHCA due to hanging. We excluded patients for the following reasons: (i) failure to measure rSO_2 and HbI (n = 11); and (ii) ROSC in the prehospital setting (n = 1). One patient fell into both categories. Finally, 21 patients were eligible for our analysis.

The patient characteristics are shown in Table 1. In the freshwater drowning group, all patients who received a blood test had hemolysis and had chest X-ray photograph (Xp) and/or chest computed tomography (CT) findings that would be expected to be observed in a drowning patient. .In the control group, some patients had Xp

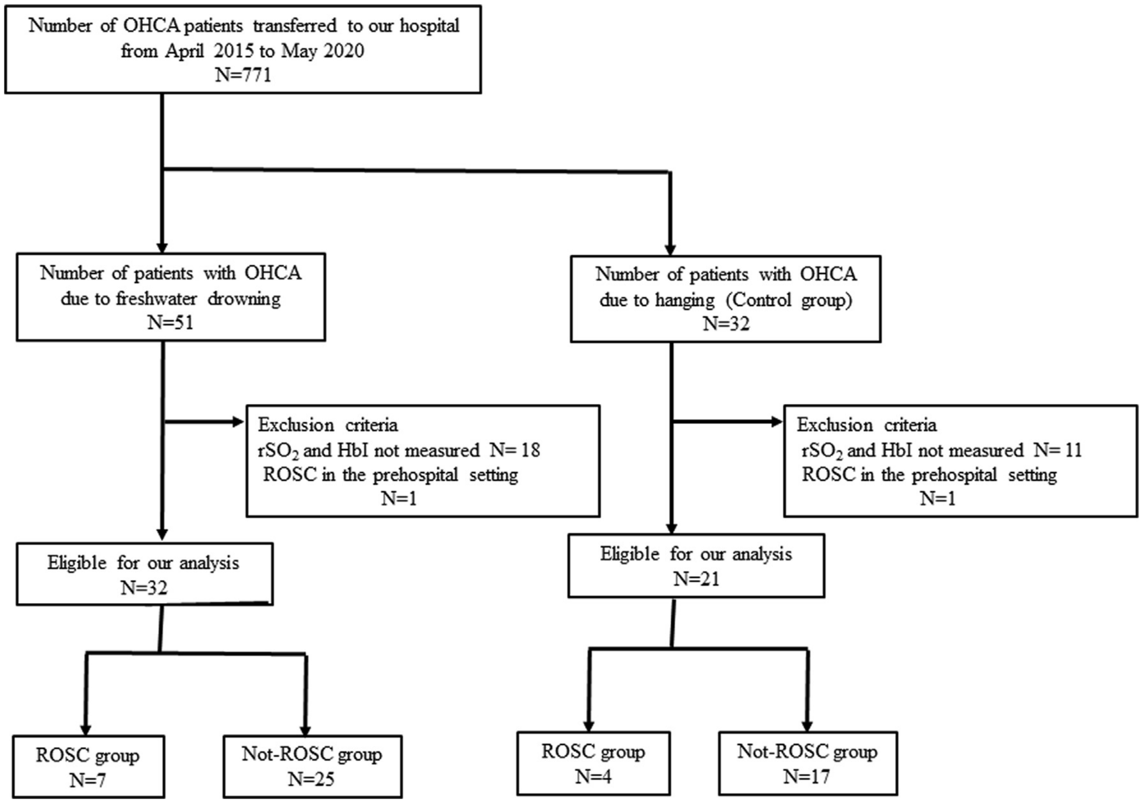

Fig. 1 – Patient flow OHCA, out-of-hospital cardiac arrest; rSO_2, regional saturation of oxygen; ROSC, return of spontaneous circulation; HbI, hemoglobin index.

and/or CT findings that were similar to those that would be expected in a drowning patient; however, these patients experienced CPA due to hanging. Therefore, their findings were thought to be due to inhalation or negative pressure pulmonary edema. In the freshwater drowning group, 30 patients were detected during Ofuro bathing, and 2 patients were detected in freshwater river, 1 patient was detected in waterway. And, in freshwater drowning group, body temperature at hospital arrival was not significantly difference between ROSC group and non-ROSC group (35.6, IQR 32.6-37.2 vs 36.6, IQR 35.6-38.0, p = 0.422).

Comparison of the changes of the HbI and rSO_2 values in the ROSC non-ROSC groups

Fig. 2 compares the change of HbI values between the ROSC and non-ROSC groups. In the freshwater drowning group, the HbI values during resuscitation in the ROSC group were significantly decreased in comparison to the non-ROSC group (−0.28 [IQR −0.55, −0.12] vs. −0.04 [IQR −0.16, 0.025]; p = 0.024), and the change in the HbI values in all patients with an ROSC was negative (Fig. 2A). In other words, in the freshwater drowning group, the HbI values decreased in all patients with an ROSC. In the control group, no significant difference was detected between the ROSC and non-ROSC groups (0.11 [IQR −0.3525, 0.4225] vs. −0.02 [IQR −0.14, 0.605]; p = 0.8228) (Fig. 2B).

Supplementary Fig. 1 compares the change of the rSO_2 values during resuscitation between the ROSC and non-ROSC groups. In the freshwater drowning group, the change of rSO_2 in the ROSC group was significantly greater than that in the non-ROSC group (15.6 [IQR 8.7, 28.8] vs. 0.3 [IQR −0.75, 3.25]; p = 0.0004) (Supplementary Fig. 1A). In the control group, the change of rSO_2 in the ROSC group was also significantly greater than that in the non-ROSC group (15.85 [IQR 14.375, 20.85] vs. 0 [IQR -1, 2.2]; p = 0.0027) (Supplementary Fig. 1B).

Comparison of the change of HbI and rSO_2 values before and after an ROSC or the termination of CPR in each patient with OHCA

Fig. 3 shows the change of HbI values between before and after an ROSC or the termination of CPR in each patient with OHCA in the freshwater drowning and control groups. In the non-ROSC group, we compared the value at ER admission with before termination of CPR.

In the freshwater drowning group, the HbI values of patients with an ROSC were significantly decreased after the ROSC in comparison to before the ROSC (1.2±0.5 vs. 0.9±0.5]; p = 0.0156) (Fig. 3A). In the non-ROSC patients, the HbI values were significantly decreased before leaving the ER in comparison to the time of ER admission (1.4±0.3 vs. 1.3±0.3]; p = 0.0487) (Fig. 3B).

In the control group, among patients with an ROSC no significant difference was in the HbI values before and after the ROSC (3.7±1.3 vs. 3.8±1.4]; p = 0.7940) (Fig. 3C). In the control group, among the non-ROSC patients, no significant difference was not detected in the HbI values at ER admission and before leaving the ER (2.4 ±0.6 vs. 2.6±0.7]; p = 0.2028) (Fig. 3D).

On the other hand, among patients with an ROSC, the rSO_2 values were significantly increased after the ROSC in comparison to before the ROSC in both the freshwater drowning group (60.9±3.4 vs. 40.9±3.4]; p = 0.0156) (Supplementary Fig. 2A) and the control

Table 1 – Characteristics of patients between freshwater drowning and control group

	Freshwater drowning group		p Value	Control group		p Value
	ROSC group (N = 7)	Not-ROSC group (N = 25)		ROSC group (N = 4)	Not-ROSC group (N = 17)	
Sex, n (%)						
Male	4 (57.1)	10 (40.0)	0.419	3 (75.0)	8 (47.1)	0.314
Age, years, median (IQR)	79 (68-82)	80 (73.5-85)	0.349	39.5 (27-49)	46 (21.5-69.5)	0.622
Initial rhythm, n (%)			0.315			N.A.
VF	0 (0)	1 (4.0)		0 (0)	0 (0)	
PEA	2 (28.6)	2 (8.0)		0 (0)	0 (0)	
Asystole	5 (71.4)	22 (88.0)		4 (100)	17 (100)	
Witness, n(%)			N.A.			N.A.
+	0 (0)	0 (0)		0 (0)	0 (0)	
–	7 (100)	25 (100)		4 (100)	17 (100)	
Bystander CPR, n (%)			0.593			0.549
+	3 (42.9)	8 (32.0)		3 (75.0)	10 (58.8)	
–	4 (57.1)	17 (68.0)		1 (25.0)	7 (41.2)	
Defibrillation by ELT, n (%)			0.44			N.A.
+	0 (0)	2 (8.0)		0 (0)	0 (0)	
–	7 (100)	23 (92.0)		4 (100)	17 (100)	
Administration of adrenaline by ELT, n (%)			0.628			0.463
+	2 (28.6)	5 (20.0)		1 (25.0)	2 (11.8)	
-	5 (71.4)	20 (80.0)		3 (75.0)	15 (88.2)	
Initial rhythm at ER, n (%)			0.912			0.0022
VF	0 (0)	0 (0)		0 (0)	0 (0)	
PEA	1 (14.3)	4 (16.0)		2 (50.0)	0 (0)	
Asystole	6 (85.7)	21 (84.0)		2 (50.0)	17 (100)	
Hemolysis, n (%)			0.198			0.0071
+	7 (100)	20 (80.0)		0 (0)	10 (58.8)	
-	0 (0)	0 (0)		4 (100)	3 (17.7)	
Not tested	0 (0)	5 (20.0)		0 (0)	4 (23.5)	
Xp and/or CT findings suspected to drowning, n (%)			N.A.			0.0015
+	7 (100)	25 (100)		1 (25.0)	16 (94.1)	
–	0 (0)	0 (0)		3 (75.0)	1 (5.9)	
Body tempature at hospital arrival, median (IQR)	35.6 (32.6-37.2) (N = 7)	36.6 (35.6-38.0) (N = 20)	0.422	35.6 (35.3-36.2) (N = 4)	34.4 (33.7- 35.2) (N = 14)	0.0092
Survival, n (%)	0 (0)	0 (0)	N.A.	1 (25.0)	0 (0)	0.0346

CPR, cardiopulmonary resuscitation; CT, computed tomography; ELT, emergency life-saving technician; IQR, interquartile range; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; rSO_2, regional saturation of oxygen; VF, ventricular fibrillation; Xp, X-ray photograph.

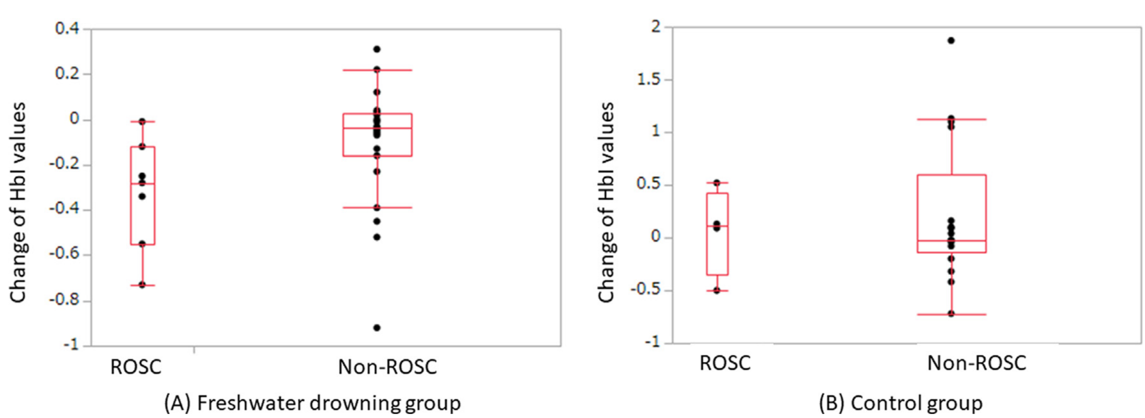

Fig. 2 – Comparison of the change of HbI values between the ROSC and non-ROSC groups (A) Freshwater drowning group. (B) Control group. ROSC, return of spontaneous circulation; HbI, hemoglobin index.

group (71.0±3.4 vs. 54.0±3.3]; $p = 0.0029$) (Supplementary Fig. 2C). However, among non-ROSC patients, no significant difference was detected between ER admission and before leaving the ER in either the freshwater drowning group (42.6±1.8 vs. 44.3±1.8]; $p = 0.1617$)

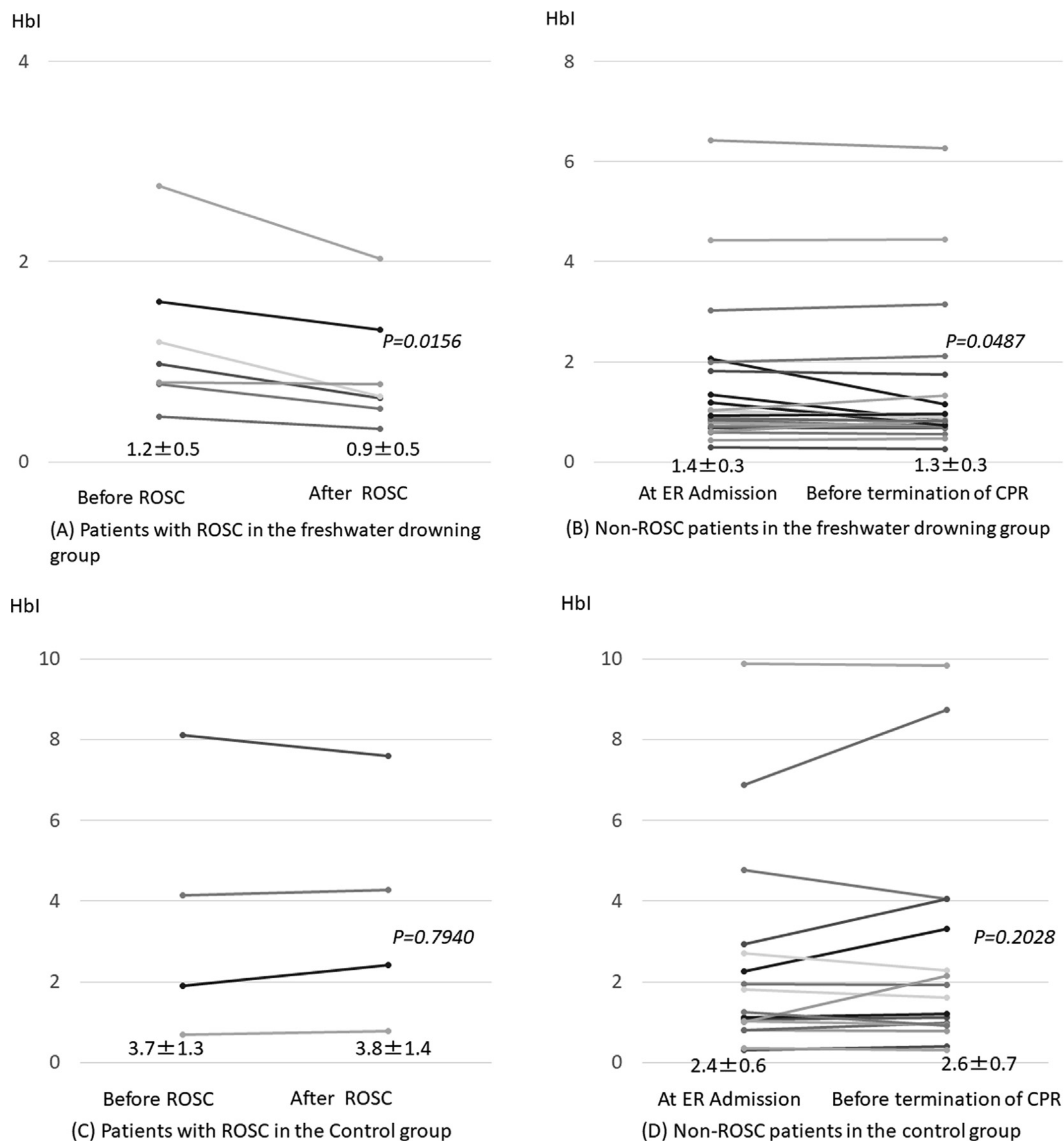

Fig. 3 – Comparison of the change of HbI values between before and after ROSC or the termination of CPR in each patient with OHCA (A) Patients with an ROSC in the freshwater drowning group. (B) Non-ROSC patients in the freshwater drowning group. (C) Patients with an ROSC in the control group. (D) Non-ROSC patients in the control group. In the non-ROSC groups (B and D), we compared the value at ER admission with the value before the termination of CPR. OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; HbI, hemoglobin index; ER, emergency room; CPR, Cardiopulmonary resuscitation.

(Supplementary Fig. 2B) or the control group (48.6±1.6 vs. 48.7 ±1.7]; $p = 0.8333$) (Supplementary Fig. 2D).

Serial change in the HbI and rSO_2 values of in a patient in the freshwater drowning group who obtained an ROSC

We showed a representative case of the serial changes in the HbI and rSO_2 values of a patient in the freshwater drowning group who obtained an ROSC (Fig. 4). The patient was a 73-year-old man took a bath after drinking. He was found in the bathtub with his head completely submerged, and emergency services were contacted. An emergency life-saving technician (ELT) recognized a CPA, with initial ECG showing asystole (witness [-] and bystander CPR [+]). The ELT start CPR, and he was transferred to our hospital 39 minutes after the call. ROSC was not obtained in the prehospital setting. His HbI value gradually decreased from the time he appeared to obtain ROSC (Fig. 4. Red arrow). The ROSC status was checked every 2 minutes; thus, his heart actually started to move shortly before the rhythm check. His rSO_2 values began to increase with the ROSC, which is in line with previous reports [2,6]. His hemodynamics were unstable after the ROSC, and physicians recognized asystole again. They restarted CPR, and he soon obtained an ROSC. At the second ROSC, there was no change in the HbI values.

Discussion

Based on our analysis of the changes of the HbI values during resuscitation in patients with OHCA due to freshwater drowning, we

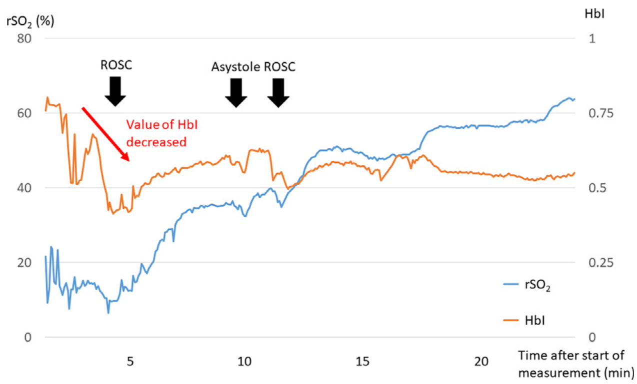

Fig. 4 – Serial change of HbI and rSO_2 in a representative patient with an ROSC in the freshwater drowning group HbI, hemoglobin index; ROSC, return of spontaneous circulation; rSO_2, regional saturation of oxygen.

believed that this study revealed the hemodilution induced by freshwater drowning in real time. To our knowledge, this is the first report to analyze the evaluation of hemodilution induced by freshwater drowning using continuous measurement of HbI values. In addition to providing information on the basic pathophysiology of patients after freshwater drowning our findings may help to improve the severity assessment and treatment of patients after freshwater drowning.

In this study, the HbI values were decreased in all patients in the freshwater drowning group who obtained an ROSC (Fig. 2A, 3A). In freshwater drowning, the blood is considered to be diluted [10,11]. In an autopsy study on freshwater drowning Zátopková et al. performed hemolytic staining of the endocardium of the left heart chambers, and reported that the endocardium of the right heart chambers was clear and transparent [15]. They reported that this staining was due to hypo-osmolar hemolysis, which occurs in the left heart chambers and systemic circulation after hypotonic fluid passes across the alveolocapillary membrane [15]. Even good quality CPR is usually only equivalent to approximately 15-25% of cardiac output [16]. Thus, we thought that the decreased HbI values in all patients in the freshwater drowning group who obtained an ROSC reflects that diluted blood in the left heart chambers flowed into the brain immediately after the ROSC was obtained.

Dilution by infusion during resuscitation might have affected the decrease in HbI. However, no significant change was seen in the HbI values of the patients in the control group (Fig.2B, 3C, 3D). We could not find any literature on the dilution of blood into the brain by infusion during resuscitation. A study on the effects of infusion during resuscitation on cerebral blood flow, reported that fluid loading (11 ml/kg, i.v.) during CPR improved cardiac output (34% increase), while left ventricular perfusion decreased to 74% and brain flow decreased to 65% of control in 18 euvolemic dogs with induced CPA [17]. Ditchey and Lindenfeld found that volume loading during CPR in euvolemic dogs reduced cerebral and coronary blood flow due to increases in right atrial diastolic pressure and intracranial pressure that surpassed the increases in aortic systolic and diastolic pressure [18]. Infusion during resuscitation might reduce cerebral blood flow from previous studies [17,18]. Rebet et al. reported that no significant relationship was found between changes in Hb and HbI following fluid challenge after cardiac surgery [19]. Taken together, we thought that the cerebral blood flow does not increase during resuscitation, and that the effect of fluid loading on HbI was also limited. In this study, no significant change in HbI was seen in the control group (Fig.2B, 3C, 3D). Thus, we considered that the effect of dilution by fluid infusion was limited. We would like to examine the effects of infusion in the future, since the effect of the volume of infusion was not examined in this study.

The rSO_2 values began to increase with ROSC, as was shown in previous studies (Supplementary Figs. 1, 2A, 2C) [2–7]. The increase in rSO_2 means that the spontaneous movements of the heart have returned and that oxygenated blood is flowing into the brain. We showed a representative case of the serial changes in the HbI and rSO_2 values of a patient in the freshwater drowning group who obtained an ROSC (Fig. 4). The decrease in the HbI values after the ROSC, despite the increase of rSO_2, indicated that blood was diluted by freshwater drowning as the heart began to move to the brain. The reason why HbI started to drop before the first ROSC was that the pulse check was performed every 2 minutes, and it is possible that the heart started to move spontaneously before the pulse check. We thought that the HbI did not change before or after the second ROSC because the blood diluted after the first ROSC had already been distributed to the whole body. We believed that we could observe the blood dilution induced by freshwater drowning in real time using the HbI values of patients with OHCA due to freshwater drowning.

The present study was associated with some limitations. First, this was a retrospective single center study. It is necessary to collect data prospectively on a large scale. Second, all patients included in this study had OHCA. Third, in this study, we defined freshwater drowning by the patient's face being completely submerged when they were found. CPA might have been induced by causes other than freshwater drowning. Fourth, the effect of infusion has not been evaluated in this study, since there are few cases in which the amount of infusion during resuscitation was accurately described. Fifth, no drowning in salt water was included in this study since our hospital is far from the coast. Sixth, many drowned patients during Ofuro bathing were included. Ofuro bathing is a component of Japan's national culture and identity. Ministry of Health, Labour and Welfare in Japan reported that Sudden death while taking a bath was considered to be a fatal condition due to an increase in body temperature and impaired consciousness due to hypotension, which makes it difficult to take a bath and further increases the body temperature [20]. Further research is needed to determine whether the results of this study are valid for general interpretation.

Conclusion

In patients with an ROSC in the freshwater drowning group, all HbI values were decreased after ROSC. We might detect blood dilution induced by freshwater drowning in real time by the retrospective reanalysis of HbI data which we previously obtained by near-infrared spectroscopy. The measured hemodilution was of no measurable clinical significance. To prove the validity of this research's result, further prospective large study is needed.

Funding

This work was supported by JSPS KAKENHI Grant Number JP19H03758.

CRediT authorship contribution statement

Tomoya Hirose: Formal analysis, Writing – original draft. **Tomohiko Sakai:** Methodology, Investigation, Data curation. **Ryosuke Takegawa:** Validation. **Mitsuo Ohnishi:** Validation. **Jotaro Tachino:** Investigation. **Arisa Muratsu:** Investigation. **Shunichiro Nakao:** Investigation. **Tadahiko Shiozaki:** Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2021.100179.

REFERENCES

[1] Takegawa R, Hayashida K, Rolston DM, et al. Near-infrared spectroscopy Assessments of regional cerebral oxygen saturation for the prediction of clinical outcomes in patients with cardiac arrest: a review of clinical impact, evolution, and future directions. Front Med 2020;7 587930.
[2] Nakahori Y, Hirose T, Shiozaki T, et al. Serial changes in values of cerebral regional saturation of oxygen (rSO_2) during resuscitation in patients with out-of-hospital cardiac arrest. Nihon Kyukyu Igakukai Zasshi 2013;24:774–80.
[3] Ogawa Y, Shiozaki T, Hirose T, et al. Load-distributing-band cardiopulmonary resuscitation for out-of-hospital cardiac arrest increases regional cerebral oxygenation: a single-center prospective pilot study. Scand J Trauma Resusc Emerg Med 2015;23:99.
[4] Hirose T, Shiozaki T, Nomura J, et al. Pre-hospital portable monitoring of cerebral regional oxygen saturation (rSO_2) in seven patients with out-of-hospital cardiac arrest. BMC Res Notes 2016;9:428.
[5] Ehara N, Hirose T, Shiozaki T, et al. The relationship between cerebral regional oxygen saturation during extracorporeal cardiopulmonary resuscitation and the neurological outcome in a retrospective analysis of 16 cases. J Intensive Care 2017;5:20.
[6] Takegawa R, Shiozaki T, Ogawa Y, et al. Usefulness of cerebral rSO_2 monitoring during CPR to predict the probability of return of spontaneous circulation. Resuscitation 2019;139:201–7.
[7] Sakai T, Hirose T, Shiozaki T, et al. Pre-hospital portable monitoring of cerebral regional oxygen saturation (rSO_2) by ambulance personnel during cardiopulmonary resuscitation: A prospective observational analysis of 87 cases in Osaka city, Japan. *Resuscit Plus* 2021;6 100093.
[8] Mori N, Hirose T, Shiozaki T, et al. Effectiveness of the hemoglobin index for screening of subarachnoid hemorrhage in out-of-hospital cardiopulmonary arrest patients: a retrospective observational study. Acute Med Surg 2020;7 e450.
[9] Myers D, McGraw M, George M, et al. Tissue hemoglobin index: a non-invasive optical measure of total tissue hemoglobin. Crit Care 2009;13(Suppl 5):S2.
[10] Byard RW, Cains G, Simpson E, et al. Drowning, haemodilution, haemolysis and staining of the intima of the aortic root– preliminary observations. J Clin Forensic Med 2006;13:121–4.
[11] Feldhaus KM. Submersion. In: Marx J, Hockberger R, Walls R, editors. Rosen's Emergency Medicine: Concepts and Clinical Practice. Maryland Heights, MO: Mosby; 2002. p. 2050–4.
[12] Richards DB. Chapter 137 Drowning. In: Walls RM, editor. Rosen's Emergency Medicine: Concepts and Clinical Practice E-Book. PA: Philadelphia; 2018. p. 5346–57.
[13] Bierens JJ, Lunetta P, Tipton M, et al. Physiology of drowning: A review. Physiology 2016;31:147–66.
[14] Nakagawa E, Minamitani H, Ochiai R, et al. A new system for noninvasive measurement of cerebral regional oxygen supply. In: *Engineering in Medicine and Biology Society 1997. Proceedings of the 18th Annual International Conference of the IEEE*. p. 194–5.
[15] Zátopková L, Hejna P, Janík M. Hemolytic staining of the endocardium of the left heart chambers: a new sign for autopsy diagnosis of freshwater drowning. Forensic Sci Med Pathol 2015;11:65–8.
[16] Duggal C, Weil MH, Gazmuri RJ, et al. Regional blood flow during closed-chest cardiac resuscitation in rats. J Appl Physiol 1993;74:147–52.
[17] Voorhees 3rd WD, Ralston SH, Kougias C, et al. Fluid loading with whole blood or Ringer's lactate solution during CPR in dogs. Resuscitation 1987;15:113–23.
[18] Ditchey RV, Lindenfeld J. Potential adverse effects of volume loading on perfusion of vital organs during closed-chest resuscitation. Circulation 1984;69:18118–9.
[19] Rebet O, Fischer MO, Zamparini G, et al. Near-Infrared Spectroscopy Hemoglobin Index Measurement During Fluid Challenge: A Prospective Study in Cardiac Surgery Patients. J Cardiothorac Vasc Anesth 2015;29:924–9.
[20] Ministry of Health, Labour and Welfare in Japan. Research on understanding the actual situation of bathing-related accidents and preventive measures. https://www.mhlw.go.jp/stf/shingi/2r9852000002rkou-att/2r9852000002rkv5.pdf9 (Accessed 9 October 2021). In Japanese.