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Clinical paper

Study on the timing of severe blood-brain barrier disruption using cerebrospinal fluid-serum albumin quotient in post cardiac arrest patients treated with targeted temperature management

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Abstract

Aim: We aimed to evaluate the onset of severe blood-brain barrier (BBB) disruption using cerebrospinal fluid/serum albumin quotient (Qa) in cardiac arrest patients treated with target temperature management (TTM).

Methods: This was a prospective single-centre observational cohort study from October 2017 to September 2018 with the primary endpoint being the onset of severe BBB disruption, determined based on Qa in cardiac arrest patients treated with TTM. Enrolled patients were grouped according to neurologically good and poor outcomes using the cerebral performance category (CPC) at 3 months after return of spontaneous circulation (ROSC). Severe BBB disruption was evaluated using Qa measured immediately (Qa_0) and at 24 h (Qa_{24}), 48 h (Qa_{48}), 72 h (Qa_{72}) after ROSC.

Results: Of 21 patients enrolled, poor outcome group had 10 patients. Qa_0 was 0.019 (0.008∼0.024) in the poor outcome group and 0.006 (0.003∼0.008) in the good outcome group ($p = 0.09$). Qa_{24} was 0.045 (0.025∼0.115) in the poor outcome group and 0.006 (0.003∼0.006) in the good outcome group ($p = 0.03$). Qa_{48} was 0.055 (0.023∼0.276) in the poor outcome group and 0.006 (0.006∼0.009) in the good outcome group ($p = 0.02$). Qa_{72} was 0.047 (0.026∼0.431) in the poor outcome group and 0.007 (0.005∼0.011) in the good outcome group ($p = 0.02$).

Conclusion: Qa was significantly higher in the poor outcome group at 24 h, 48 h, and 72 h. Severe BBB disruption indicated by Qa $\geq$ 0.02 in poor outcome group treated with TTM occurred within the first 24 h after ROSC.

Keywords: Cardiac arrest, Prognostication, Albumin

Abbreviations: BBB, blood brain barrier; Qa, cerebrospinal fluid and serum albumin quotient; TTM, targeted temperature management; ROSC, restoration of spontaneous circulation; CPR, cardiopulmonary resuscitation; CA, cardiac arrest; CSF, cerebrospinal fluid; CPC, Cerebral Performance Categories; GCS, Glasgow coma scale; LP, lumbar puncture; ICP, intracranial pressure.

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Introduction

Brain injury following cardiopulmonary resuscitation (CPR) is a significant cause of morbidity in survivors. One of the most serious complications following cardiac arrest is brain oedema, which is associated with poor neurologic outcome and death.[1–3] Therefore, international guidelines recommend the use of targeted temperature management (TTM) for reducing the complications following return of spontaneous circulation (ROSC).[4]

Brain oedema includes cytotoxic oedema and vasogenic oedema; while cytotoxic oedema results primarily from cerebral ischaemia, vasogenic oedema results from reperfusion[3] Ischaemic insult decreases the tight junction integrity between the endothelial cells in the brain, causes the breakdown of the blood-brain barrier (BBB), and directly contributes to the brain vasogenic oedema.[5,6] A study demonstrated that cardiac arrest (CA) resulted in brain oedema development one hour after ROSC in an 8-minute asphyxiation model of CA in rats.[3] Another study demonstrated that global cerebral ischaemia following CA resulted in BBB disruption and oedema 24 h after ROSC in a pig model.[7] Permanent brain oedema after ROSC following severe BBB disruption is predictive of poor neurologic outcome.[8–11] Therefore, the treatment to preserve BBB before its disruption is important in terms of neurologic outcome.

However, to the best of our knowledge, there is no study on the onset of severe BBB disruption in CA patients treated with TTM. We aimed to evaluate the onset of severe BBB disruption by using the cerebrospinal fluid-serum albumin quotient (Qa), which is widely accepted as the gold standard for the functional assessment of BBB disruption,[12] in post-CA patients treated with TTM.

Methods

This study was approved by the Institutional Review Board of Chungnam National University Medical Centre (CNUH IRB 2017-10-027)

Study design and patients

This was a prospective single-centre observational cohort study conducted from October 2017 to September 2018 on patients who had been treated with TTM following CA. The primary endpoint was to evaluate the onset of severe BBB disruption using Qa in post-CA patients treated with TTM.

The neurologic status of the patients was obtained during the 3-month follow-up after CA.[13] Neurological outcome was assessed using the Glasgow-Pittsburgh cerebral performance categories (CPC) scale. The CPC scale scores were graded as CPC 1 (good performance), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), or CPC 5 (brain death or death). The good outcome group was defined as a CPC 1 or 2, and the poor outcome group as a CPC between 3 and 5. Cerebral performance categories (CPC) 1 and 2 had good outcomes, whereas CPC 3–5, without return to normal social activity, had poor outcomes.[14] Resuscitated out-of-hospital CA patients with Glasgow coma scale (GCS) score ≤ 8 after ROSC and patients who underwent TTM were included in the study. The exclusion criteria for this study were as follows: (1) <18 y of age, (2) traumatic CA or interrupted TTM (due to hemodynamic instability), (3) not eligible for TTM (i.e., intracranial haemorrhage, active bleeding, known terminal illness, or poor pre-arrest neurological status), (4) ineligible for lumbar puncture (LP) (i.e., brain computed tomography showed severe cerebral oedema, obliteration of the basal cisterns, occult intracranial mass lesion, or coagulopathy), (5) on extracorporeal membrane oxygenation, (6) unable to consent to LP, and (7) refusal of further treatment by the next of kin.

TTM protocol

TTM was applied using cooling devices (Arctic Sun® Energy Transfer Pads TM, Medivance Corp., Louisville, USA). The target temperature of 33 °C was maintained for 24 h with rewarming to 36.5 °C at the rate of 0.25 °C/h and was monitored using an oesophageal and bladder temperature probe. Sedatives and analgesics were used during TTM and patients received standard care according to the protocol described in a previous study.[15] Anti-epileptic medications were administered as soon as a seizure was suspected either clinically or through EEG.

Data collection

The following data were collected from the database: age, sex, presence of a witness at the time of the collapse, bystander CPR, first monitored rhythm, aetiology of cardiac arrest, time from collapse to CPR (no flow time), time from CPR to ROSC (low flow time), time from ROSC to obtaining intracranial pressure (ICP) via LP (ICP time), GCS after ROSC, and CPC at 3 months after ROSC.

Obtaining of CSF via lumbar catheter

The procedure was performed with the patient lying in the lateral decubitus position with hips and knees flexed. A lumbar catheter was inserted using a Hermetic™ lumbar accessory kit (Integra Neurosciences, Plainsboro, NJ, USA) in the patients, and ICP via lumbar catheter was measured using a manometer. ICP was measured as immediate (ICP_0), and at 24 h (ICP_{24}), 48 h (ICP_{48}), and 72 h (ICP_{72}) after ROSC. Cerebrospinal fluid (CSF) albumin and serum albumin were obtained as immediate, and at 24 h, 48 h, and 72 h after ROSC. Severe BBB disruption was evaluated using Qa values on immediate (Qa_0), 24 h (Qa_{24}), 48 h (Qa_{48}), and 72 h (Qa_{72}) after ROSC as follows: Qa values > 0.02 indicated severe BBB disruption.[16]

Sample size

We planned to enrol 20 patients based on the mentioned inclusion and exclusion criteria because no previous study has reported the use of Qa in evaluation of severe BBB disruption in post-CA patients treated with TTM.

Statistical analysis

We reported continuous variables as median with interquartile range or as mean and standard deviation depending on the normal distribution. Categorical variables were reported as frequencies and percentages. Comparisons between the two groups were made using the chi-square test, Fisher's exact test, the Mann-Whitney U test, or two-tailed *t*-test. All statistical analyses were performed using the PASW/SPSSTM software, version 18 (IBM Inc., Chicago, USA). Results were considered significant at $P < 0.05$.

Results

Characteristics of study subjects

Of the 33 post-CA patients in whom ROSC was achieved, 21 patients were enrolled in the study. While 11 patients were in the good outcome group, 10 were in the poor outcome group (Fig. 1). The mean age, no flow time, sequential organ failure assessment score, and ICP time were not significantly different between the two groups. Of the 21 enrolled patients, 11 (52.38%), 0 (0.00%), 0 (0.00%), 5 (23.81%) and 5 (23.81%) patients had CPC 1, 2, 3, 4 and 5, respectively (Table 1).

Comparison of intracranial pressure between poor and good outcome groups

ICP_0 was 210 (145∼227) mmH_2O in the poor outcome group and 158 (126∼164) mmH_2O in the good outcome group ($p = 0.02$). ICP_{24} was 230 (213∼241) mmH_2O in the poor outcome group and 144 (138∼160) mmH_2O in the good outcome group ($p < 0.001$). ICP_{48} was 248 (234∼250) mmH_2O in the poor outcome group and 160 (146∼176) mmH_2O in the good outcome group ($p < 0.001$). ICP_{72} was 251 (228∼264) mmH_2O in the poor outcome group and 168 (142∼190) mmH_2O in the good outcome group ($p < 0.001$) (Table 2).

Comparison of cerebrospinal fluid/serum albumin quotient between poor and good outcome groups

Qa_0 was 0.019 (0.008∼0.024) in the poor outcome group and 0.006 (0.003∼0.008) in the good outcome group ($p = 0.09$). Qa_{24} was 0.045 (0.025∼0.115) in the poor outcome group and 0.006 (0.003∼0.006) in the good outcome group ($p = 0.03$). Qa_{48} was 0.055 (0.023∼0.276) in the poor outcome group and 0.006 (0.006∼0.009) in the good outcome group ($p = 0.02$). Qa_{72} was 0.047 (0.026∼0.431) in the poor outcome group and 0.007 (0.005∼0.011) in the good outcome group ($p = 0.02$) (Table 2, Fig. 2).

Discussion

In this study, ICP measured as immediate, and at 24 h, 48 h, and 72 h after ROSC were significantly higher in the poor outcome group. Qa obtained immediately after ROSC was not significantly different between both the groups. However, Qa was significantly higher in the poor outcome group at 24 h, 48 h, and 72 h. There was no severe BBB disruption in the good outcome group; however, the poor outcome group showed severe BBB disruption in 24 h, 48 h, and 72 h after ROSC in post-CA treated with TTM. In addition, neurological outcomes were found to be poor in all patients with severe BBB disruption ($Qa > 0.02$), and Qa was a valuable tool to evaluate the neurologic outcomes in post CA patients treated with TTM.

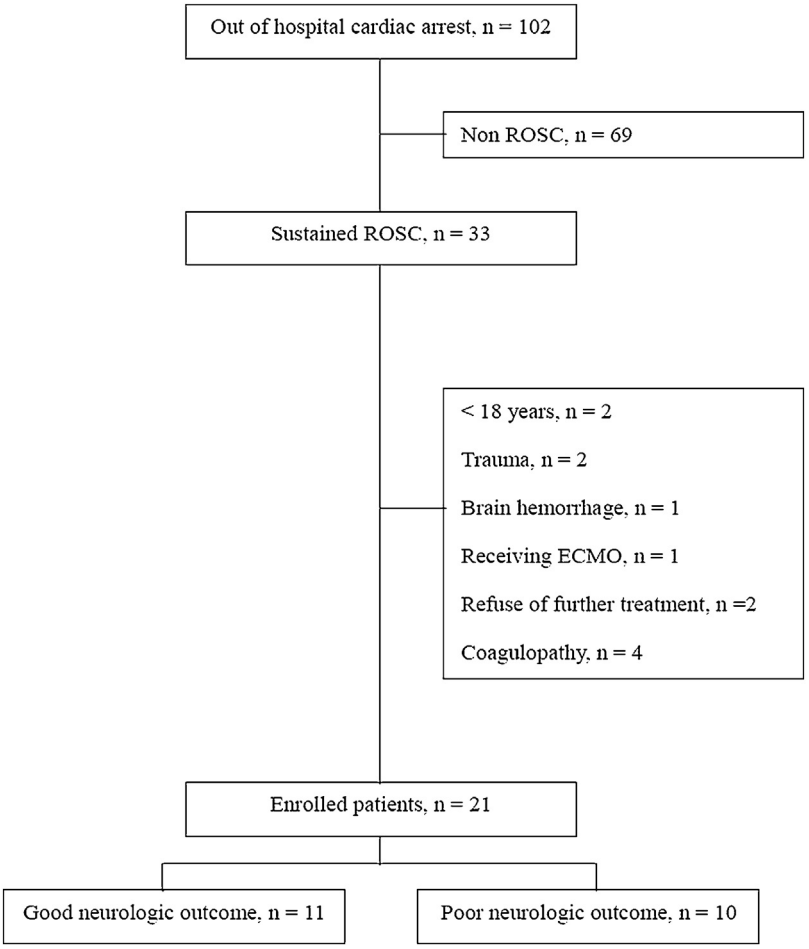

Fig. 1 – Flowchart of the study (ROSC: return of spontaneous circulation; ECMO: extracorporeal membrane oxygenation).

Table 1 – General characteristics and comparison of study population between poor and good outcome groups.

Characteristics		Total	Good outcome	Poor outcome	P value
Age (years)		57.00(41.50~71.50)	63.00(39.00~74.00)	53.00(41.75~72.25)	0.78
Sex, n (%)	Male	14(66.67)	8(72.73)	6(60.00)	0.54
	Female	7(33.33)	3(27.27)	4(40.00)	
Witness, n (%)	Yes	15(71.43)	9(81.82)	6(60.00)	0.27
	No	6(28.57)	2(18.18)	4(40.00)	
Bystander CPR, n (%)	Yes	15(71.43)	10(90.91)	5(50.00)	0.04
	No	6(28.57)	1(9.09)	5(50.00)	
Initial rhythm, n (%)	Asystole	6(28.57)	0(0.00)	6(60.00)	0.009
	PEA	8(38.10)	5(45.45)	3(30.00)	
	VF	5(23.81)	5(45.45)	0(0.00)	
	Pulseless VT	1(4.76)	0(0.00)	1(10.00)	
	Unknown	1(4.76)	1(9.09)	0(0.00)	
Causes, n (%)	Hypoxia	14(66.67)	6(54.55)	8(80.00)	0.21
	Arrhythmia	3(14.29)	3(27.27)	0(0.00)	
	Unknown	4(19.05)	2(18.18)	2(20.00)	
GCS, n (%)	3	16(76.19)	7(63.64)	9(90.00)	0.27
	4	1(4.76)	0(0.00)	1(10.00)	
	5	1(4.76)	1(9.09)	0(0.00)	
	6	2(9.52)	2(18.18)	0(0.00)	
	7	1(4.76)	1(9.09)	0(0.00)	
SOFA score		6.00(4.00~8.00)	5.00(3.00~7.00)	6.50(5.75~8.00)	0.52
No flow time (min)		2.00(0.00~8.50)	0.00(0.00~5.00)	2.00(0.00~13.00)	0.45
Low flow time (min)		18.00(9.50~30.00)	10.00(5.00~20.00)	27.00(14.75~37.75)	0.005
ICP time (h)		4.67(3.92~5.72)	4.28(3.82~6.10)	5.02(4.06~5.43)	0.55

Continuous variables expressed as median (interquartile range). CPR, cardiopulmonary resuscitation; GCS, Glasgow coma scale; ICP, intracranial pressure; SOFA, sequential organ failure assessment; PEA, pulseless electrical activity; VF, ventricular fibrillation, VT, ventricular tachycardia.

Table 2 – Comparison of intracranial pressure and cerebrospinal fluid-serum albumin quotient between poor and good outcome groups.

Values	Total	Good outcome	Poor outcome	P value
Sa_0 (g/dl)	3.60(3.05~3.80)	3.70(3.20~3.90)	3.40(2.35~3.70)	0.05
Sa_{24} (g/dl)	3.20(3.05~3.60)	3.40(3.10~3.70)	3.05(2.12~3.22)	0.006
Sa_{48} (g/dl)	3.00(2.80~3.20)	3.10(3.00~3.30)	2.90(2.78~3.03)	0.02
Sa_{72} (g/dl)	3.10(2.80~3.40)	3.30(3.00~3.60)	3.00(2.70~3.13)	0.02
Ca_0 (g/dl)	0.030(0.018~0.050)	0.021(0.012~0.030)	0.050(0.030~0.082)	0.03
Ca_{24} (g/dl)	0.038(0.019~0.131)	0.020(0.010~0.022)	0.131(0.061~0.375)	0.04
Ca_{48} (g/dl)	0.053(0.020~0.160)	0.020(0.019~0.029)	0.160(0.064~0.871)	0.03
Ca_{72} (g/dl)	0.040(0.021~0.145)	0.022(0.019~0.032)	0.145(0.082~1.285)	0.04
ICP_0 (mmH_2O)	160(138~215)	158(126~164)	210(145~227)	0.02
ICP_{24} (mmH_2O)	179(142~230)	144(138~160)	230(213~241)	<0.001
ICP_{48} (mmH_2O)	201(159~248	160(146~176)	248(234~250)	<0.001
ICP_{72} (mmH_2O)	201(163~251)	168(142~190)	251(228~264)	<0.001
Qa_0	0.008(0.005~0.019)	0.006(0.003~0.008)	0.019(0.008~0.024)	0.09
Qa_{24}	0.012(0.006~0.045)	0.006(0.003~0.006)	0.045(0.025~0.115)	0.03
Qa_{48}	0.019(0.006~0.055)	0.006(0.006~0.009)	0.055(0.023~0.276)	0.02
Qa_{72}	0.013(0.007~0.047)	0.007(0.005~0.011)	0.047(0.026~0.431)	0.02

Continuous variables expressed as median (interquartile range). Sa, serum-albumin measured on immediate (Sa_0), 24 h (Sa_{24}), 48 h (Sa_{48}), and 72 h (Sa_{72}); Ca, cerebrospinal fluid-albumin measured on immediate (Ca_0), 24 h (Ca_{24}), 48 h (Ca_{48}), and 72 h (Ca_{72}); ICP, intracranial pressure measured on immediate (ICP_0), 24 h (ICP_{24}), 48 h (ICP_{48}), and 72 h (ICP_{72}); Qa, cerebrospinal fluid-serum albumin quotient measured on immediate (Qa_0), 24 h (Qa_{24}), 48 h (Qa_{48}), and 72 h (Qa_{72}).

BBB regulates the movement of plasma constituents into the brain parenchyma.[17,18] BBB comprises of the cerebral microvascular endothelial cells, a capillary basement membrane, pericytes, and astrocyte end-feet.[19,20] The junctional complexes between endothelial cells comprise tight junctions and adherens junctions.[18] Hypoxia increases the permeability of BBB tight junctions and leads to BBB disruption.[21–27] Li et al. demonstrated that global cerebral ischaemia following CA resulted in BBB disruption and oedema at 24 h after ROSC in a swine model study.[28] Although several studies on the methods to preserve BBB such as methylene blue, fingolimod, and TTM have been reported, most have been conducted on animal or chronic disease models. Methylene blue, associated with partial inhibition of nitric oxide synthase activity, reduces BBB disruption and subsequent

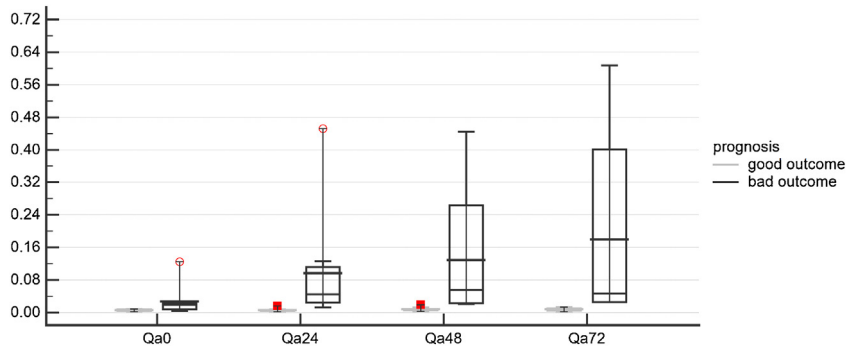

Fig. 2 – The box plot shows the change in cerebrospinal fluid-serum albumin quotient on immediate (Qa_0), 24 h (Qa_{24}), 48 h (Qa_{48}), and 72 h (Qa_{72}) after ROSC in poor and good outcome groups (Qa: cerebrospinal fluid-serum albumin quotient).

neurologic injury in a piglet model.[29] Fingolimod in multiple sclerosis is assumed to prevent BBB disruption.[30] TTM can reduce the expression of inflammatory mediators and free radical generation,[31,32] and improve neurologic outcomes.[33–35] In this study of patients treated with TTM, while severe BBB disruption began 24 h after ROSC, ICP obtained immediately after ROSC was significantly higher in the poor outcome group. The results demonstrated higher ICP following global cerebral ischaemia immediately after ROSC, and severe BBB disruption began at 24 h after ROSC in the poor outcome group treated with TTM. Therefore, the treatments to preserve BBB in post-CA treated with TTM should be applied within 24 h after ROSC, and future studies are needed to focus on how to preserve BBB.

There were several limitations in our study. First, this was single centre study. Second, other biomarkers such as neuron specific enolase were not measured. Therefore, we could not speculate the change in these parameters. Third, we did not assess the histopathologic and cellular changes in the brain cortex after ROSC. Fourth, we measured Qa intermittently, and not continuously. Therefore, it was impossible to know at what point during the first 24 h that BBB disruption occurred. Fifth, CSF-albumin was obtained through a lumbar catheter and not from the cerebral ventricle. But, Qa, calculated using the CSF/serum-albumin, is a reliable parameter to indicate BBB disruption as CSF-albumin is blood-derived protein. Finally, we did not consider the age-dependent CSF flow rate. Future studies are needed to focus on this limitation.

Conclusion

Qa was significantly higher in the poor outcome group at 24 h, 48 h, and 72 h. Severe BBB disruption indicated by Qa $\geq$ 0.02 in poor outcome group treated with TTM occurred within the first 24 h after ROSC.

Conflict of interest statement

The authors have no conflict of interest to report.

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None.

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