

# 学位論文

Association of brain metabolites with blood  
lactate and glucose levels with respect to  
neurological outcomes after out-of-hospital  
cardiac arrest: a preliminary microdialysis study

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Clinical paper

## Association of brain metabolites with blood lactate and glucose levels with respect to neurological outcomes after out-of-hospital cardiac arrest: A preliminary microdialysis study<sup>☆</sup>

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## ABSTRACT

**Aim:** Out-of-hospital cardiac arrest (OHCA) is associated with poor prognosis. Cerebral microdialysis (CMD) is an efficient sampling technique to detect neurochemical changes in brain interstitial tissue. In this retrospective study, we hypothesised that there are different CMD levels between patients with favourable and unfavourable neurological outcomes.

**Methods:** Data of patients with OHCA admitted to Kagawa University Hospital and administered therapeutic hypothermia (TH) were collected. Using a CMD probe, extracellular glucose, lactate and pyruvate levels were measured hourly along with intracranial perfusion pressure (ICP) and cerebral perfusion pressure (CPP) for the initial 72 h during TH. The lactate/pyruvate (LP) ratio was calculated. Patients were divided into favourable [Glasgow–Pittsburgh cerebral performance category 1–2 at 30 days after cardiac arrest] or unfavourable neurological outcome groups. CMD biochemical markers and blood lactate and glucose levels were compared between two groups.

**Results:** Ten patients were included. ICP was significantly higher in the unfavourable than in the favourable neurological outcome group; there were no significant differences with respect to CPP. The CMD LP ratio in the unfavourable outcome group progressively increased; significant differences were observed on days 2, 3 and 4 ( $p < 0.01$ ). Significant differences in blood lactate levels were observed between the groups only on day 3.5. CMD and blood glucose levels were higher in the unfavourable than in the favourable outcome group during TH.

**Conclusion:** The association of CMD levels with long-term outcomes would be better defined in a large randomised prospective study.

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## Introduction

Out-of-hospital cardiac arrest (OHCA) is associated with poor prognosis. Predicting neurological outcomes in these patients is complicated mainly because of the uncertainty in the evaluation of brain damage.<sup>1–3</sup> Cerebral microdialysis (CMD) is an efficient sampling technique to detect neurochemical changes in brain interstitial tissue and has been evaluated in patients with traumatic brain injury<sup>4–7</sup> intracerebral haematoma<sup>8</sup> and subarachnoid haemorrhage to monitor brain metabolism<sup>9,10</sup>; however, there are only few reports of CMD studies in patients with OHCA,<sup>11–14</sup> and

the association of CMD metabolites (i.e. brain metabolites) with blood lactate and glucose with respect to neurological outcomes in patients with non-traumatic OHCA remains unknown. The aim of this study was to examine the hypothesis that there are different CMD levels between patients with favourable and unfavourable neurological outcomes in patients with non-traumatic OHCA treated with therapeutic hypothermia (TH).

## Methods

*Study design and setting*

This study is a retrospective analysis of prospectively collected data of patients admitted to Kagawa University Hospital who received therapeutic hypothermia (TH) after resuscitation from OHCA between 1 July, 2005 and 30 April, 2009. This study was

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approved by the institutional review board of the Kagawa University Hospital (Heisei 16-035) and conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from patients' legally authorised representative prior to inclusion.

The Kagawa university hospital is an academic tertiary care centre with 613 beds and 20 intensive care beds. It is also a referral centre supporting a region with a population of approximately 150,000 people. Approximately 3–5 OHCA patients are treated with TH in our ICU each year.

#### Study participants and inclusion criteria

Patients  $\geq 18$  years who were comatose after resuscitation from non-traumatic cardiac arrest and received TH were included. They were excluded if they received only comfort care within 24 h of admission. Further, patients without agreement from their family or who had no neurosurgeon available to perform the procedure were excluded. The attending physician was responsible in deciding whether the CMD was initiated. All patients with CMD sampling underwent complete TH without withdrawal of ICU care.

#### Cerebral microdialysis

In the operating room, commercially available sterile CMA 70 microdialysis catheters (CMA Microdialysis, Solna, Sweden) were placed through a burr hole. The microdialysis catheters were inserted in the right frontal subcortical white matter. After positioning, a cranial computed tomography scan was conducted to verify the location of the catheter and check for any catheter-related intracranial bleeding. The catheters were attached to a CMA 106 perfusion pump, and central nervous system sterile isotonic perfusion fluid (CMA Microdialysis) was perfused at a rate of 0.3  $\mu\text{L}/\text{min}$ . After an equilibration period of 2–4 h, samples were collected hourly and immediately analysed for glucose, lactate and pyruvate using a CMA 600 microdialysis analyser (CMA Microdialysis). CMD data are presented as real sample concentrations, uncorrected for recovery. For CMD, recovery has been estimated to be approximately 70%.

#### Therapeutic hypothermia

Core temperature was monitored using bladder or rectal temperature upon hospital admission and monitored during the cooling period. A target core temperature of 32–34°C was maintained for 24 h, followed by gradual rewarming for 24–48 h.

A sedative drug [midazolam (0.2–0.4 mg/kg/h)] and an analgesic [pentazocine (120 mg/day)] was usually administered. A muscle relaxant [vecuronium (0.05 mg/kg/h)] was also administered during the induction and maintenance phases, as deemed necessary. Sedatives and analgesics were usually tapered off, once patients had been rewarmed to 36°C.

Regarding glucose control, intervention was usually initiated when the blood glucose level was  $>200$  mg/dL. Insulin was administered and adjusted as needed by each physician.

As for ICP management, mannitol was administered by each physician as needed. CMD metabolites were just collected for research use, and the clinical decision was not changed based on the results of the CMD metabolites.

#### Data sampling

The following data were collected: the number of measurements, age, sex, time from collapse to recovery of spontaneous circulation (ROSC), Glasgow coma scale (GCS) score on admission, cardiac arrest of cardiac origin, density of regions of interest (ROIs)

and grey/white matter ratio (GWR) on brain CT obtained within 2 h after ROSC, details of drugs used during TH and Glasgow–Pittsburgh cerebral performance category (GP-CPC) [15] at 30 days after cardiac arrest. CMD metabolite levels, including glucose, lactate and pyruvate, were measured hourly in addition to intracranial and cerebral perfusion pressure (ICP and CPP) for the initial 72 h. The lactate/pyruvate (LP) ratio was also calculated and adopted instead of the direct value of lactate due to the nature of CMD. The tentative normal value was defined as CMD glucose level of  $>0.7$  mmol/L [4,16,17].

#### Density of measurement in brain CT obtained within 2 h after ROSC

As reported by Lee et al. [18], circular ROIs (9.4 mm<sup>2</sup>) were used to measure the densities of grey matter (GM) and white matter (WM) in Hounsfield units. The average densities of GM were measured in the putamen, while those of WM were measured in the corpus callosum.

#### Outcome measures

The primary outcome measure was the association of CMD metabolites with blood lactate and glucose levels with respect to neurological outcomes at 30 days after cardiac arrest. The secondary outcome measure was the association of ICP with the CMD LP ratio with respect to neurological outcomes. A favourable neurological outcome was defined as GP-CPC 1–2; an unfavourable neurological outcome was defined as GP-CPC 3–5.

#### Statistical analysis

Patients were divided into two groups: the favourable neurological outcome group and the unfavourable neurological outcome group. The groups were compared using the Mann–Whitney *U* test or Fisher's test as appropriate.

For each patient, 12-h pooled values of CMD metabolites, blood lactate and glucose levels as well as CPP and ICP were compared between the favourable neurological outcome and unfavourable neurological outcome groups during the observation period. Furthermore, the Spearman rank correlation coefficient was calculated between ICP and the CMD LP ratio in the favourable and unfavourable neurological outcome groups. The results are presented as *n* (%) or medians (interquartile ranges, IQR). A *p* value of  $\leq 0.05$  was considered significant.

## Results

#### Comparison of baseline characteristics

During the study period, 18 comatose patients were admitted to the ICU following cardiac arrest and were treated with TH. Eight patients who met the exclusion criteria were excluded. Of the 10 patients included in this study, four were included in the unfavourable neurological outcome group; furthermore, a total of 828 measurements were included in this study (Table 1).

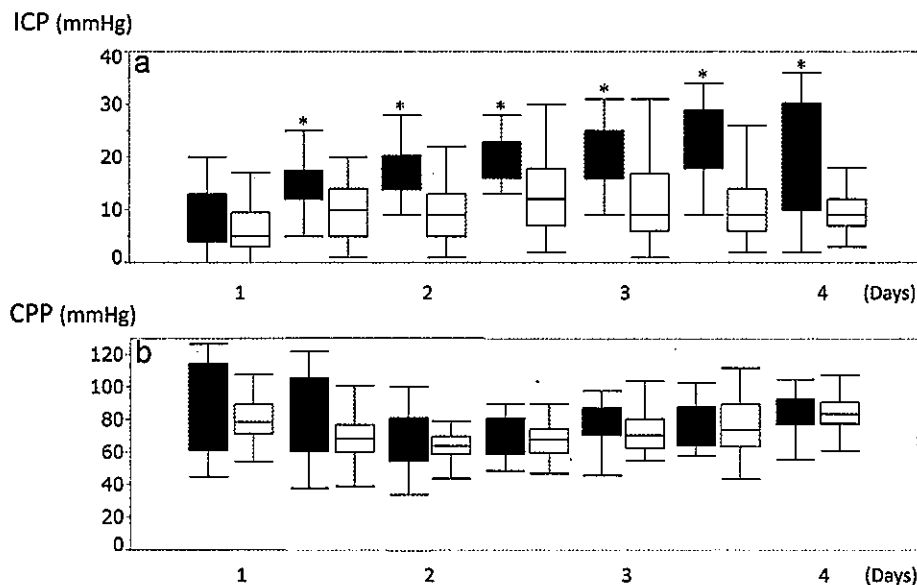
There were no significant differences between the favourable neurological outcome and unfavourable neurological outcome groups with regard to age, sex, time from collapse to ROSC, initial GCS score, the rate of cardiac arrest of cardiac origin, density of ROIs and GWR in brain CT obtained with 2 h after ROSC or details of drugs used during TH.

**Table 1**  
Comparison of baseline characteristics.

	Favourable outcome group	Unfavourable outcome group	p-Value
Patients	6	4	
CMD Measurements	492	336	
Age (years)	44 (40–48)	54 (30–74)	0.52
Sex (male)	5 (83.3)	1 (25.0)	0.19
Time from collapse to ROSC (min)	14 (11–38)	35 (17–42)	0.30
Initial GCS score	3 (3–3)	3 (3–3)	1.00
Cardiac arrest of cardiac origin	5 (83.3)	1 (25.0)	0.19
Brain CT obtained within 2 h after ROSC	5 (83.3)	3 (75)	1.00
Density of ROI (HU)			
Putamen	38 (37–38)	38 (35–40)	0.75
Corpus callosum	30 (29–31)	30 (29–32)	0.64
Gray–white matter ratio	1.24 (1.23–1.29)	1.25 (1.17–1.31)	1.00
During TH			
Midazolam use	6 (100)	4 (100)	
Pentazocine use	6 (100)	4 (100)	
Vecuronium use	6 (100)	4 (100)	
Mannitol use	1 (16.7)	0 (0)	1.00

Data are expressed as number (percentage), or median (interquartile range).

CMD, cerebral microdialysis; ROSC, return of spontaneous circulation; GCS, Glasgow Coma Scale; ROI, regions of interest; HU, Hounsfield units; TH, therapeutic hypothermia.



**Fig. 1.** Comparison of CPP and ICP between favourable and unfavourable outcome groups. (a) CPP, (b) ICP.

Twelve-hour pooled values for each patient were expressed as median [IQR], and comparisons were made between the favourable neurological outcome group and unfavourable neurological outcome group during the observation period. Patients in the unfavourable outcome group are indicated in grey, and those in favourable outcome group are indicated in white. The boxes are the 25th to 75th percentiles, and the whiskers are the 5th to 95th percentiles.

\* $p < 0.01$  compared with the favourable outcome group.

#### Comparison of intracranial and cerebral perfusion pressures between the two groups

The ICP in the unfavourable neurological outcome group were significantly higher than those in the favourable neurological outcome group during TH, whereas there were no significant differences between the groups with respect to CPP (Fig. 1a, b).

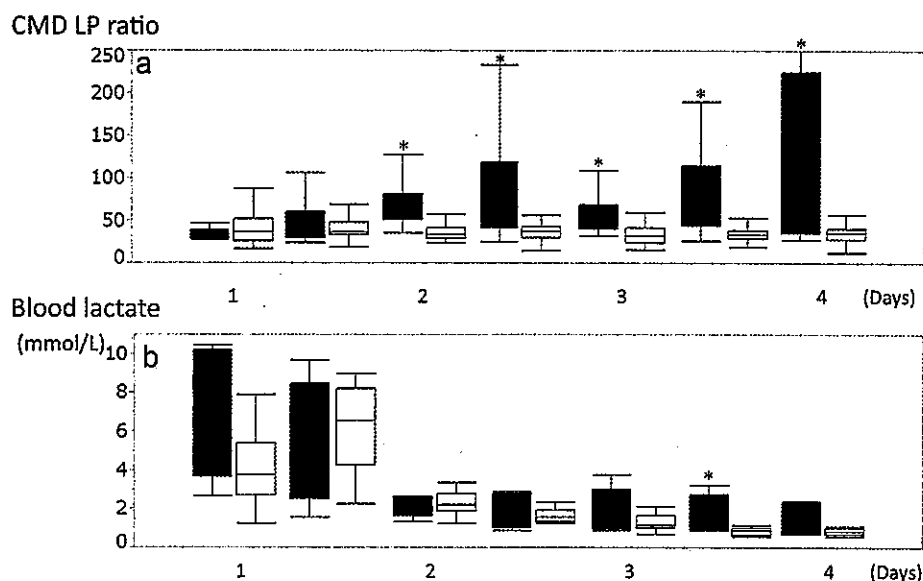
#### Comparison of ischaemia indicators between CMD and blood measurements with respect to neurological outcome

There were no significant differences between the two groups with respect to the CMD LP ratio on day 1 [median (interquartile range), 37 (30–40) vs. 36 (26–52);  $p = 0.99$ ]; however, the CMD LP ratio in the unfavourable neurological outcome group progressively increased compared with that in the favourable neurological out-

come group, and statistically significant differences were observed on days 2, 3 and 4 [65 (51–82) vs. 33 (29–42), 53 (41–69) vs. 32 (24–42), 45 (35–23) vs. 35 (28–41), respectively;  $p < 0.01$  for all] (Fig. 2a). On the other hand, there were no significant differences between the two groups with respect to blood lactate levels except on day 3.5 [1.4 (0.9–2.8) mmol/L vs. 0.9 (0.6–1.0) mmol/L;  $p < 0.01$ ] (Fig. 2b).

#### Comparison of glucose levels between CMD and blood measurements with respect to neurological outcome

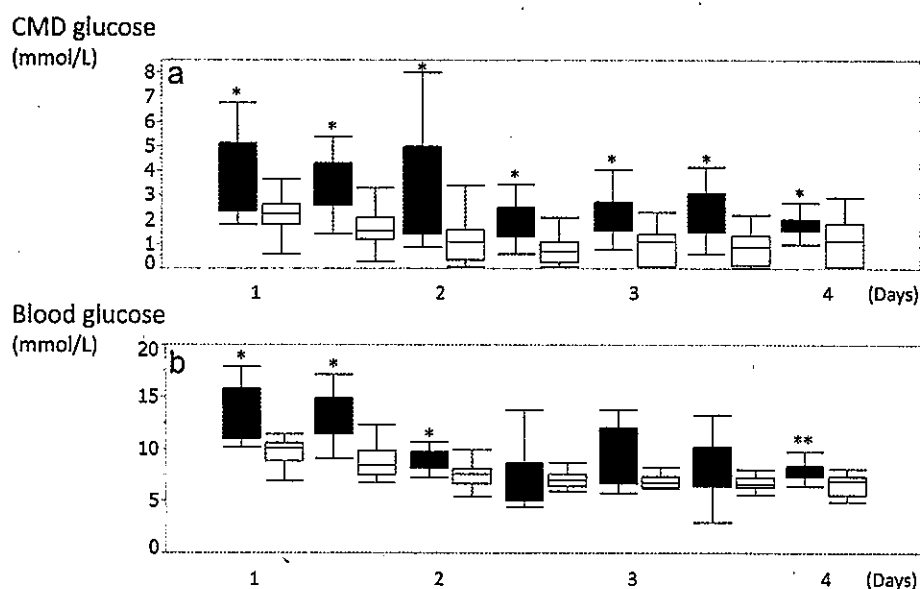
CMD glucose levels were significantly higher on day 1 in the unfavourable neurological outcome group than in the favourable outcome group [3.2 (2.4–5.2) mmol/L vs. 2.2 (1.8–2.6) mmol/L;  $p < 0.01$ ] and remained significantly high during TH [ $p < 0.01$  for all days (Fig. 3a)].



**Fig. 2.** Comparison of ischaemia indicators between brain and systemic lactate levels with respect to neurological outcome during therapeutic hypothermia. (a) LaP ratio, (b) blood lactate levels.

Twelve-hour pooled values for each patient were expressed as median [IQR], and comparisons were made between the favourable neurological outcome group and unfavourable neurological outcome group during the observation period. Patients in the unfavourable outcome group are indicated in grey, and those in the favourable outcome group are indicated in white. The boxes are the 25th to 75th percentile, and the whiskers are the 5th to 95th percentiles.

\* $p < 0.01$  compared with the favourable outcome group.



**Fig. 3.** Comparison between brain and systemic glucose levels with respect to neurological outcome during therapeutic hypothermia. (a) CaMD glucose, (b) blood glucose. Twelve-hour pooled values for each patient were expressed as median [IQR], and comparisons were made between the favourable neurological outcome group and unfavourable neurological outcome group during the observation period. Patients in the unfavourable outcome group are indicated in grey, and those in the favourable outcome group are indicated in white. The boxes are the 25th to 75th percentiles, and the whiskers are the 5th to 95th percentiles.

\* $p < 0.01$  compared with the favourable outcome group. \*\* $p < 0.05$  compared with the favourable outcome group.

As for blood glucose levels, significant differences were observed on days 1, 1.5, 2 and 4 in blood glucose level ( $p < 0.01$  for the first three days and 0.02, respectively) (Fig. 3b).

#### Association of ICP with the CMD LP ratio during TH

There was a weak negative correlation between ICP and the CMD LP ratio in the favourable neurological outcome group ( $r = -0.14$ ,  $p < 0.01$ ) (Fig. 4a). On the other hand, there was a moderate cor-

relation between ICP and the CMD LP ratio in the unfavourable neurological outcome group ( $r = 0.43$ ,  $p < 0.01$ ) (Fig. 4b).

#### Discussion

In the current study, the CMD LP ratio in the unfavourable neurological outcome group progressively increased, and significant differences were observed on days 2, 3 and 4 compared with those in the favourable neurological outcome group, whereas no signif-

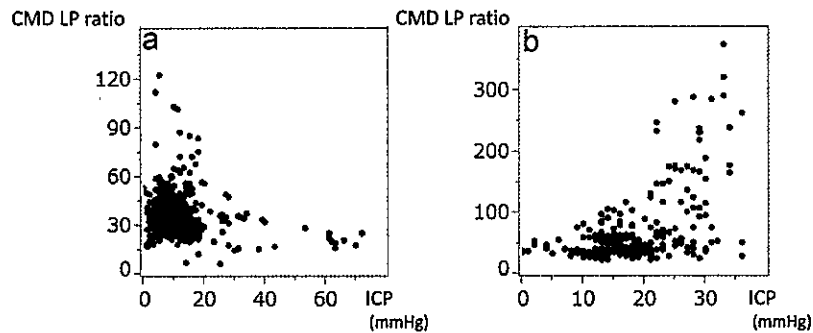


Fig. 4. Association of ICP with the CMD LP ratio during TTM in the favourable neurological outcome group (a). Association of ICP with the CMD LP ratio during TTM in unfavourable the neurological outcome group (b).

icant differences were observed initially between the two groups. On the other hand, there were no significant differences between the two groups in blood lactate levels except on day 3.5. As for glucose, both CMD glucose and blood glucose levels were higher in the unfavourable neurological outcome group than in the favourable neurological outcome group during TH in patients with OHCA.

Only one case report<sup>19</sup> of a hospitalised patient following cardiac arrest and two case series<sup>11,12</sup> in patients with OHCA examined CMD metabolites; however, the first patient reported by Bauer et al. died 5 days after resuscitation and the alteration in CMD metabolites were observed only for 10 h after resuscitation.<sup>19</sup> Pynnonen et al. reported eight cases of comatose survivors after OHCA treated with TH; however, alterations in the CMD LP ratio or CMD glucose were not reported because they focused on the effects of different carbaemic states on cerebral perfusion and metabolism.<sup>12</sup> Nordmark et al. reported four cases with good recovery who were treated with TH after OHCA, and CMD metabolites were observed for the first 3 days in one of four patients (two cases: 40-h observation, one case: 50-h observation).<sup>11</sup>

Regarding the ischaemia indicator, in three out of the four patients reported by Nordmark et al., although a completely normal CMD LP ratio (<25) was not reached during the entire observation period,<sup>4,20–23</sup> the CMD LP ratio developed a decreasing trend. Alterations in the CMD LP ratio in the four cases with good recovery were consistent with our data in the favourable outcome group; however, those were limited to favourable outcome cases. To the best of our knowledge, our details of CMD metabolites in patients with unfavourable neurological outcomes are the first reported data. An interesting finding of the current study with the small number of patients is that the CMD LP ratio may have the tendency to progressively increase in patients with unfavourable neurological outcomes, whereas systemic lactate levels maintained normal levels regardless of neurological outcomes.

Similar to other diseases such as subarachnoid haemorrhage and traumatic brain injury (TBI) where an increasing LP ratio is associated with poor outcomes,<sup>21,24,25</sup> we hypothesised that a similar effect was seen in patients with OHCA who received TH. The CMD LP ratio reflects the equilibrium between product and substrate of the reaction catalysed by lactate dehydrogenase and is a good surrogate for the cytosolic oxido-reduction status.<sup>26</sup> A high CMD LP ratio is associated with anaerobic metabolism in the brain.<sup>27</sup> One of the mechanisms considered for the progressive increase in the CMD LP ratio in the unfavourable outcome group was that brain oedema leads to cerebral hypoperfusion which increases anaerobic metabolism based on the alteration of ICP and moderate correlation between ICP and the CMD LP ratio in the unfavourable outcome group. This should mostly be seen in patients with OHCA and concomitantly elevated ICP but could theoretically also be seen in patients with OHCA having normal ICP. We found two patients with

elevated ICP (mean ICP during the study period >20 mmHg) in the unfavourable neurological outcome group; the mean CMD LP ratio was 43.6 in one patient. On the other hand, we found two patients with normal ICP in the unfavourable neurological outcome group; the CMD LP ratio was 55.9 in one patient. This may be explained by the presence of non-convulsive seizure and the difference in the dose of sedatives. We would perform prospective study to further evaluate this hypothesis.

With respect to glucose, Nordmark et al. reported that the pattern of CMD glucose levels differed among patients with good recovery, which may be explained by altered blood glucose levels in patients with OHCA.<sup>11</sup> In the current study, there was a linear relationship between CMD glucose and blood glucose levels in both groups, and those in the unfavourable outcome group were relatively higher than those in the favourable outcome group. In patients with TBI, low brain glucose is associated with unfavourable outcome.<sup>4</sup> Reductions in systemic glucose supply may induce CMD glucose levels to decrease below critical levels, leading to increased brain anaerobic metabolism,<sup>28</sup> followed by a high CMD LP ratio. On the other hand, hyperglycaemia may also promote anaerobic glycolysis, leading to extra and intracellular acidosis, accumulation of cerebral lactate and elevated CMD LP ratio.<sup>29,30</sup> Diaz-Parejo et al. proposed that a significant increase in cerebral lactate concentration is observed when hyperglycaemia exceeds 15 mmol/L and transient moderate hyperglycaemia (12–15 mmol/L) does not affect cerebral energy metabolism in patients with severe TBI.<sup>31</sup> In the current study, although blood glucose levels in the unfavourable neurological outcome group remained at 10–15 mmol/L on day 1, the rest of the blood glucose levels in both groups remained <10 mmol/L during observation period. Therefore, blood glucose levels in themselves were not considered to have a significant effect on CMD glucose levels or the CMD LP ratio in the current study. Higher cerebral extracellular glucose concentration in unfavourable neurological outcome group may be the consequence of impaired glucose uptake in the injured brain.

To examine whether CMD adds more prognostic information, we compared the results of initial CT. Lee et al. reported that the GWR on the putamen/corpus callosum with cut-off value at 1.17 can predict unfavourable neurological outcomes with a specificity of 100% on the CT obtained immediately after ROSC (median, 69.5 min).<sup>18</sup> In the current study, one patient with an initial GWR of 1.16 developed an unfavourable neurological outcome, but another patient with an initial GWR of 1.25 progressively increased the LP ratio to 280 with close monitoring during TH and developed an unfavourable neurological outcome. Thus, we believe that CMD may be a novel prognostic modality.

CMD examination in patients with post-cardiac arrest syndrome can provide significant data in clinical practice; however, it seems slightly invasive unless another cranial operation is simultaneously

required. Therefore, neurointensivists, regardless of their primary discipline, are required to have knowledge on basic neuroscience research and expertise of neurosurgery to safely obtain more clinical data.<sup>32</sup>

### Limitations

This study has several limitations. First, it was retrospectively conducted in a single centre, which introduces potential selection bias. Uncontrolled confounding factors may also exist. Second, the number of patients included in the current study was small. Approximately 250–300 patients are hospitalised in our ICU annually, which seems to make it a 'low-volume centre;' however, our ICU has played a leading role in neurocritical care in Japan.<sup>3,32,33</sup>

Third, exclusion criteria were determined; however, we could not identify the specific reason why CMD was not initiated on each excluded patient due to relatively old data.

Patients who suffered from cardiac arrest should be monitored by continuous cEEG, but in the current study, cEEG was not applied due to it being a relatively old study. Fourth, the current data seem slightly old because writing a research paper regarding CMD was suspended mainly due to the small number of study patients and complexity of understanding CMD data.

### Conclusions

The association of CMD levels with long-term outcomes would be better defined through a large randomised prospective study.

### Conflict of interest statement

None.

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