A Perspective on Post-Cardiac Arrest Syndrome

Mayuki Aibiki
Susumu Yamashita
Editors

Springer

A Perspective on Post-Cardiac Arrest Syndrome

Mayuki Aibiki · Susumu Yamashita
Editors

A Perspective on Post-Cardiac Arrest Syndrome

Springer

Editors
Mayuki Aibiki
Department of Emergency and Critical Care Medicine
Ehime University Graduate School of Medicine
Toon, Ehime, Japan

Susumu Yamashita
Department of Emergency Medicine
Tokuyama Central Hospital
Shunan, Yamaguchi, Japan

ISBN 978-981-13-1098-0 ISBN 978-981-13-1099-7 (eBook)
https://doi.org/10.1007/978-981-13-1099-7

Library of Congress Control Number: 2018952339

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

We pose a perspective by presenting new Japanese studies regarding PCAS (post-cardiac arrest syndrome), which had been defined as the system failure after whole-body ischemia-reperfusion injuries in the 2008 ILCOR statement [1]. For the targeted readers such as emergency physicians, intensivists, cardiologists, neurologists, and the others treating PCAS patients, we provide several recent topics of PCAS: (1) non-convulsive status epilepticus with neuromonitoring during TTM; (2) the timing of the crucial treatments for PACS, PCI, and TTM; (3) the early predictions for survival and neurological outcome by lactate clearance in post-cardiac arrest survivors; (4) TTM indication for suffocation cases; and (5) a stricter outcome prediction using physiological parameters for post-cardiac arrest victims, which all could facilitate the readers to do future research in this field. Furthermore, we summarize and make editors' comments on each topic for the purpose of the readers' better understanding of the book.

Dr. Kazuhiro Sugiyama et al., Tokyo Metropolitan Bokuto Hospital, described the analysis of non-convulsive status epilepticus using amplitude electroencephalography (aEEG) in post-cardiac arrest patients. They found that approx. 10% of post-cardiac arrest patients being monitored with aEEG exhibited a pattern of non-convulsive seizures and further found that a patient of them recovered to CPC-1. This continuous monitoring with aEEG is used for the early detection of epileptic episodes, and would be quite beneficial especially during TTM, in which sedatives, narcotics, and even neuromuscular blockade will be given. Furthermore, the authors showed that a single bipolar frontal hairline lead could work well if physicians aim to explore the generalized seizures, which would be approvable also to the other medical staff.

Dr. Yuji Hosoda et al., National Cerebral and Cardiovascular Center, presented a detailed comparison of neurological outcomes between PCI-first and TTM-first strategies in OHCA patients with a presumed cardiac origin. They concluded that in the present multi-center registry study, the timing of PCI did not significantly affect neurological outcome and survival in OHCA patients although PCI-first strategy delayed the induction of TTM. These results give a chance of discussions regarding topical heart cooling or systematic induced hypothermia during PCI, otherwise

normothermia during the intervention for the myocardial protection in PCAS patients [2, 3].

Dr. Kei Hayashida et al., Keio Gijyuku University, showed that the early lactate clearance is associated with improved outcomes of post-cardiac arrest syndrome. This topic supports a previous report describing an association of neuromuscular blockade usage with an early clearance of serum lactate with favorable neurological outcomes in OHCA survivors [4, 5]. Also, the current results might show, at least in part, the importance of hemodynamic optimization in the survivors of cardiac arrest.

Dr. Yutaka Sakuda et al., Okinawa Kyodo Hospital, focused on the indication of targeted temperature management in patients after choking or suicide hanging. The authors evaluated such cases treated with therapeutic hypothermia. Although all patients had poor outcomes in their study, several previous case reports showed recoveries to CPC 1or 2, whose conditions were discussed with the experienced cases of this study. The authors proposed to seek criteria of selecting right victims from near or exact suffocation for the indication of TTM. Indeed, a recent larger registry study of 692 victims reported that hanging patients with cardiac arrest had worse outcome than non-cardiac arrest patients; cardiac arrest patients with TTM had worse unadjusted survival and neurologic outcome than non-TTM patients, which might be due to the variety of TTM implementation [6]. This recent study might support Dr. Sakuda's proposal.

Dr. Mitsuaki Nishikimi et al., Nagoya University, Department of Emergency and Intensive Care Medicine, proposed a potential stricter prediction score, CAST (post-cardiac arrest syndrome for therapeutic hypothermia) or cCAST (condensed CAST) score, in neurological outcomes in cardiac arrest patients before inducing targeted temperature management. CAST score is calculated by eight parameters including initial rhythm, ROSC duration, GCS motor scale, and gray matter to white matter attenuation ratio. The authors validated both scores on sensitivity and specificity and concluded that cCAST score is more accurate to predict a poor outcome in PCAS patients.

Finally, we, as the editors, express our appreciation to all the authors for their time and vigorous efforts on valuable studies.

Ehime, Japan — Mayuki Aibiki
Yamaguchi, Japan — Susumu Yamashita

References

1. Neumar RW, et al. Cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation, Circulation. 2008;118:2452–83.
2. Suzuki M, et al. An inspection of therapeutic hypothermia preceding coronary reperfusion in patients with a cardiogenic shock complicating anterior ST-segment elevation myocardial infarction. Int J Cardiol Heart Vasc. 2015;8:108–113.

3. Dae M, et al. Effects of endovascular cooling on infarct size in ST-segment elevation myocardial infarction: a patient-level pooled analysis from randomized trials. J Interv Cardiol. 2017. https://doi.org/10.1111/joic.12485. [Epub ahead of print].
4. Lee TR, et al. Better lactate clearance associated with good neurologic outcome in survivors who treated with therapeutic hypothermia after out-of-hospital cardiac arrest. Crit Care. 2013;17:R260.
5. Salciccioli JD, et al. Continuous neuromuscular blockade is associated with decreased mortality in post-cardiac arrest patients. Resuscitation. 2013;84:1728–33.
6. Hsu CH, et al. EAST Multicenter trial on targeted temperature management for hanging-induced cardiac arrest. J Trauma Acute Care Surg. 2018. https://doi.org/10.1097/TA.0000000000001945. [Epub ahead of print].

Contents

Chapter 1
A Single-Center Study on Nonconvulsive Status Epilepticus After Cardiac Arrest

Kazuhiro Sugiyama and Yuichi Hamabe

Abstract The prognostication of post-cardiac-arrest patients remains a challenge. Electroencephalography (EEG) is a promising modality; however, conventional EEG is difficult for non-neurologists to interpret. Amplitude-integrated EEG (aEEG) is quantitative EEG that is easy to interpret. aEEG is derived from continuous EEG with reduced electrode montage, with an easy setup. aEEG patterns have been useful in the prognostication of comatose post-cardiac-arrest patients. EEG is important in monitoring seizure activity in post-cardiac-arrest care. At the 44th Annual Meeting of the Japanese Society of Critical Care Medicine, we reported the incidence and characteristics of status epilepticus among patients treated with target temperature management and monitored with aEEG using a single bipolar frontal hairline lead. Seven of 61 patients (11%) revealed status epileptics, and 1 patient with continuous normal voltage before status epilepticus showed a good neurological outcome. aEEG monitoring with reduced leads has limited, but substantial, utility for detecting generalized seizure. Status epilepticus during post-cardiac-arrest care is not uniform: patients with status epilepticus are categorized into two groups based on the background pattern of aEEG before status epilepticus. Status epilepticus from continuous normal voltage is not always associated with poor outcomes. Knowledge of the background pattern can be gained, via aEEG monitoring, from the early phase after return of spontaneous circulation (ROSC). This could help identify targets of aggressive anticonvulsant therapy. Furthermore, aEEG monitoring is a useful tool for intensive and emergency physicians who treat post-cardiac-arrest patients at the bedside.

Keywords Amplitude-integrated electroencephalography · Post-cardiac-arrest care · Hypoxic encephalopathy · Prognosis · Status epilepticus

K. Sugiyama (✉) · Y. Hamabe
Tertiary Emergency Medical Center, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan

M. Aibiki, S. Yamashita (eds.), *A Perspective on Post-Cardiac Arrest Syndrome*,
https://doi.org/10.1007/978-981-13-1099-7_1

1.1 Background

1.1.1 Why Do We Need Amplitude–Integrated Electroencephalography?

The prognostication of neurological outcomes of comatose post-cardiac-arrest patients remains a challenge. Current guidelines recommend treatment with at least 24 h of target temperature management (TTM), and patients need to be sedated during TTM. Prognosis based on neurological examination needs to be delayed in patients treated with TTM. Early prognostication is ideal to customize post-cardiac-arrest care for each patient. Several modalities are useful in early prognostication, including conventional or continuous electroencephalography (EEG), which is an extensively studied promising test. EEG recordings in post-cardiac-arrest patients are crudely classified as benign or malignant. The malignant pattern includes complete or near-complete suppression, burst suppression, generalized periodic discharge, status epilepticus, and the absence of reactivity to stimuli. These patterns predict a poor neurological outcome. The normal continuous pattern, diffuse slow pattern with reactivity to stimuli, and lack of malignant pattern are relatively benign and associated with good neurological outcomes [1–4]. However, conventional EEG or continuous EEG (cEEG) is difficult for non-neurologists to interpret. Furthermore, standardization of the interpretation is not sufficient, and there are substantial interobserver differences. In some sophisticated centers, cEEG recordings are interpreted by neurologists online immediately. To the best of our knowledge, there is no center that uses this system in Japan; most emergency and intensive care physicians engaged in post-cardiac-arrest care are not familiar with interpreting EEG. We need some modalities to use cEEG recordings in real time at the bedside.

1.1.2 What Is Amplitude–Integrated Electroencephalography?

There is a trend to quantify EEG recordings and make interpretation easier for non-neurologists. Amplitude-integrated EEG (aEEG) is a type of quantitative EEG that may provide a solution.

aEEG features the amplitude of conventional EEG and is usually derived from one or two EEG channels with reduced electrode montage. aEEG has been used widely in neonatal care. In this field, electrodes are placed at the C3, C4, P3, and P4 positions of the international 10–20 system. In adults, the use of the single frontal hairline lead is reported, in addition to C3, C4, P3, and P4. The minimum and maximum amplitudes in a short period are displayed as longitudinal bandwidths. aEEG uses a band-pass filter that removes extremely low and high frequencies to avoid artifacts. The upper and lower limits of the band show the maximum and minimum amplitudes, respectively. Amplitudes of <10 μV and >10 μV are displayed on linear

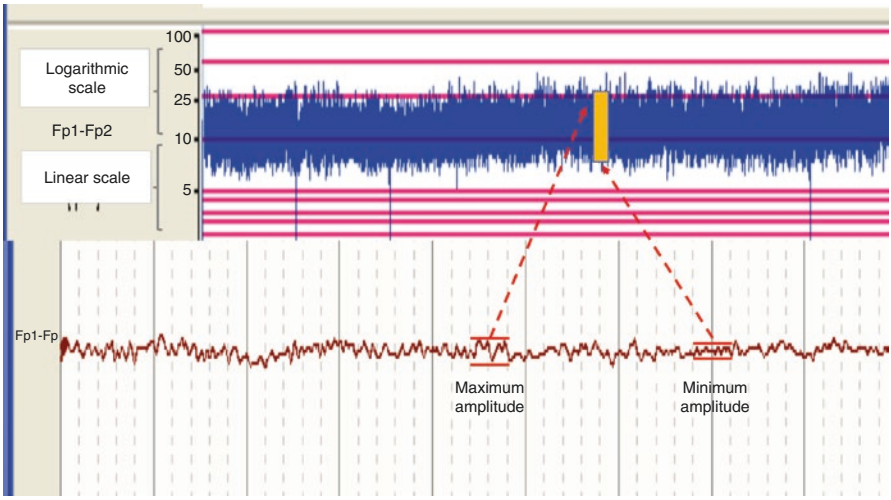


Fig. 1.1 Scheme of an amplitude-integrated electroencephalography. The minimum and maximum amplitudes in a short period are displayed as longitudinal bandwidths. The upper and lower limit of the bands shows the maximum and minimum amplitudes, respectively. Amplitudes <10 and > 10 μV are displayed on linear and logarithmic scales, respectively. These bands are arranged with a compressed timescale, which is usually 6 cm/h

and logarithmic scales, respectively. This semilogarithmic scale helped detect small changes at lower amplitudes and avoid overloading the display at higher amplitudes. These bands are arranged using a compressed timescale, which is typically 6 cm/h (Fig. 1.1). Therefore, reviewing longer periods of hours or days is possible. The reduced simplified montage is set up easily and acceptable in the busy environment of intensive care. In addition, the simplified information from the cEEG and compressed timescale enables physicians to interpret and monitor brain function in patients continuously at the bedside.

Raw EEG traces are available in modern devices, and it is important to refer to the raw trace to avoid any misinterpretation caused by noise. Furthermore, raw EEG traces can assist with the interpretation of seizure activity.

1.1.2.1 aEEG in Neonatal Care

aEEG traces are classified into patterns according to background activity. Physicians can monitor brain function by recognizing these simple patterns. Several classification systems have been suggested for use with neonates. In neonatal care, the gestational age significantly affects EEG. Sleep-wake cycling plays an important role in interpreting brain function together with background activity. Hellstrom et al. have developed a classification that consists of five background patterns, that is, continuous, discontinuous, burst suppression, low voltage, and flat. In their classification, the sleep-wake cycle and seizure are also considered [5]. aEEG is useful

in predicting the neurological outcome of hypoxic encephalopathy in neonates. A randomized trial that evaluated the efficacy of hypothermia in neonates with hypoxic encephalopathy used aEEG pattern as part of the inclusion criteria of the study [6]. In addition, aEEG is useful in detecting status epilepticus. Seizure activity displays as abrupt rises in the lower and upper margin of the band in aEEG traces. The raw EEG is referenced to confirm seizure activity.

1.1.2.2 aEEG in Adult Post–Cardiac–Arrest Care

Recently, aEEG patterns have been reported as useful in adult post-cardiac-arrest care. Rundgren et al. monitored comatose post-cardiac-arrest patients with aEEG from admission to the intensive care unit during the completion of therapeutic hypothermia. They classified aEEG patterns into four simple background patterns: continuous, suppression burst, flat, and status epilepticus (Fig. 1.2). The aEEG was created from two bipolar channels. They measured aEEG in 100 patients: 29 of 31 (90%) with continuous aEEG patterns at the start of monitoring, and 54 of 62 patients (87%) at normothermia (36 h after cardiac arrest) gained consciousness. No patients who exhibited suppression-burst patterns at registration and normothermia regained consciousness. Flat aEEG patterns at registration were not associated with poor neurological outcomes; however, flat patterns at normothermia were more associated with poor outcomes [7].

Oh et al. monitored consecutive aEEG in 55 comatose post-cardiac-arrest patients with different methods from those used by Rundgren et al. They monitored aEEG using the bipolar frontal hairline lead. In addition, they applied the neonatal care classification system of aEEG with more detailed voltage criteria. They classified aEEG patterns into continuous normal voltage (CNV), discontinuous normal voltage (DNV), low voltage (LV), burst suppression, and status epilepticus (Fig. 1.3). The continuous pattern classification used by Rundgren et al. included the CNV, DNV, and LV patterns used by Oh et al. In their study, 16 of 17 patients (94%) with CNV at the start of monitoring had a cerebral performance category (CPC) score of

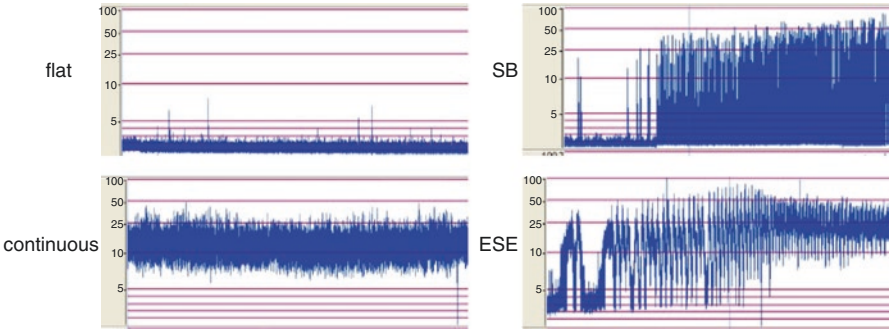


Fig. 1.2 Classification of the pattern of amplitude-integrated electroencephalography, as previously described in Rundgren et al. *SB* suppression burst; *ESE* electrographic status epilepticus

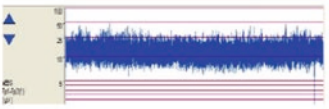
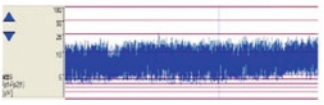
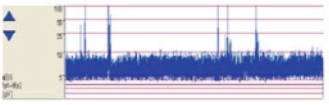
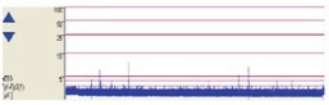
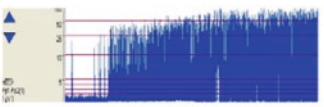
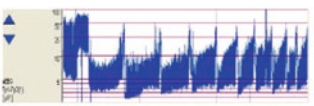
Continuous normal voltage		Maximum >10 μV Minimum >5 μV
Discontinuous normal voltage		Maximum >10 μV Minimum ≤5 μV
Low voltage		Maximum ≤10 μV
Flat		Isoelectric activity
Burst suppression		Bursts of high voltage >25 μV Absent activity <2 μV
Status epilepticus		Diagnosed together with raw electroencephalography trace

Fig. 1.3 Classification of the pattern of amplitude-integrated electroencephalography, as previously described in Oh et al.

1 or 2 at hospital discharge. Conversely, all 21 patients who did not show CNV patterns during monitoring period had poor neurological outcomes [8]. These studies showed that aEEG monitoring can be performed and play an important role in the prognostication for adult post-cardiac-arrest care. aEEG patterns could predict good neurological outcomes at the very early phase after ROSC and predict poor neurological outcomes by monitoring changes in aEEG patterns. Therefore, intensivists and emergency physicians who are unfamiliar with conventional EEG can use aEEG bedside prognostication.

Considering these results, recovery of the normal aEEG trace is essential to obtaining a good neurological outcome. However, some patients who recover a normal trace after an extended period do not have a good neurological outcome. Therefore, the particular cutoff time for predicting a good neurological outcome from ROSC to recovery of a normal aEEG trace remains unknown. In infants with asphyxia, Thoresen et al. have reported that time to a normal aEEG trace is a good predictor of neurological outcomes [9].

Oh et al. prospectively studied 130 adult comatose post-cardiac-arrest patients. They found that the recovery of CNV within 24 h after ROSC was strongly associated with good neurological outcomes [10]. In a previous study, we evaluated 30 adult survivors of cardiac arrest with initial shockable rhythm and found that the optical cutoff of CNV recovery time after ROSC to predict a good neurological outcome is 23 h. These two studies report similar results and evaluated patients sedated with midazolam. Furthermore Oh et al. reported in their study that a time to normal trace from ROSC >36 h predicted a poor neurological outcome with 100% specificity.

1.1.2.3 aEEG Monitoring Methods in Adult Post–Cardiac–Arrest Care

No classification system of aEEG in adult post-cardiac arrest care has been established. Rundgren et al. have suggested a very simple classification system that is easy to understand (Fig. 1.2). Compared with this classification, Oh et al., who used the neonatal care classification system, have developed a more precise set of voltage criteria (Fig. 1.3). Moreover, this classification is still easy for non-neurologists to interpret. In the studies mentioned above, Oh et al. reported higher specificity for both good and poor neurological outcomes. This difference is related, in part, to the aEEG classification system used in both studies. Higher specificity is desirable for prognostication; therefore, we have used the classification reported by Oh et al. in our practice.

Simplicity and ease of setup are important factors in monitoring aEEG during post-cardiac-arrest care because many procedures have to be performed in this situation. The complexity of preparation could become a major barrier to monitoring cEEG. Typically, a montage with reduced electrodes is used to aid with this. Oh et al. used a bipolar channel of frontal hairline lead. They argue that this method is sufficient to monitor global brain function and is useful in prognostication. The frontal hairline lead can be positioned easily. Expert EEG technicians are not available full time in most centers in Japan; however, physicians or nurses in intensive care units (ICU) can attach the frontal hairline electrode in a very short time and set up aEEG monitoring. We use the Fp1-Fp2 bipolar channel to monitor aEEG, with disposable hydrogel electrodes (Fig. 1.4). Using this method, it is possible to begin aEEG monitoring in 5 min.

Monitoring seizure activity is another important role of cEEG. The monitoring and treatment of status epilepticus have been increasingly emphasized in post-cardiac-arrest care. Current guidelines recommend the use of frequent conventional EEG or continuous EEG to detect seizure in these patients [11, 12]. The role of aEEG in monitoring seizure in post-cardiac-arrest patients has not been established. We recently reported 65 cases that were monitored with aEEG using frontal hairline montage during post-cardiac-arrest care after ROSC at our center at the 44th annual meeting of Japanese Society of Critical Care Medicine. We evaluated the incidence and characteristics of post-cardiac-arrest patients with electrographic status epilepticus.

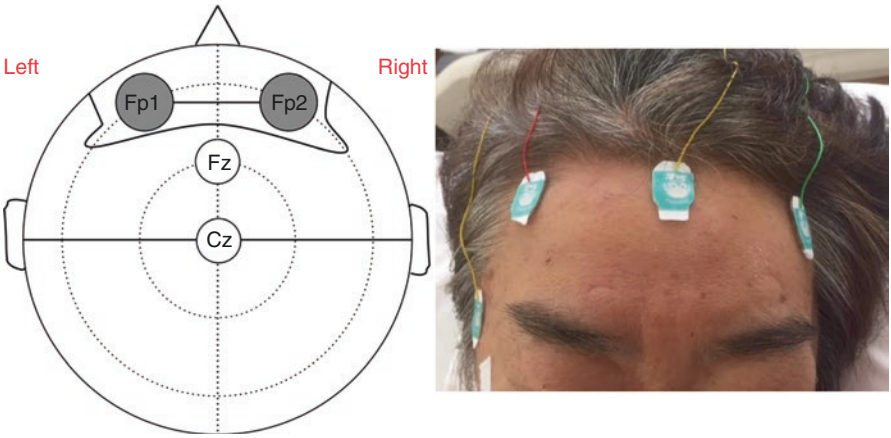


Fig. 1.4 A bipolar frontal hairline lead using disposable hydrogel electrodes

1.2 Methods

Comatose survivors after cardiac arrest who were treated with TTM and monitored with aEEG at our center from April 2013 to December 2016 were evaluated. Patients were excluded from the study if they were under 18 years of age, aEEG monitoring was not started within 24 h after ROSC, or aEEG recordings could not be interpreted because of noise.

During TTM, patients were maintained at 34 °C for 24 h and gradually rewarmed to 36 °C during the next 12 h. An external cooling system was applied as a cooling device, but the heat exchanger in circuit was used in patients treated with extracorporeal membrane oxygenation. Midazolam and fentanyl were used for sedation and analgesia, and most patients were paralyzed with vecuronium during hypothermia to control shivering. Administration of midazolam and vecuronium was stopped when the patient's temperature reached 36 °C.

We used the classification system of aEEG patterns previously described by Oh et al. (Fig. 1.3). This classification includes CNV, DNV, LV, flat, BS, and status epilepticus (SE). The aEEG monitoring was performed with bipolar channel Fp1-Fp2 (frontal hairline lead). We used the diagnostic criteria for status epilepticus previously described in the study by Rundgren et al. Status epilepticus was suspected from aEEG traces and confirmed by referencing the raw bipolar channel Fp1-Fp2 trace. There are two different diagnostic criteria for status epilepticus, from continuous background and burst suppression. In patients with a continuous pattern before status epilepticus, electrographic status epilepticus was diagnosed when the repetitive epileptiform discharge with a frequency and amplitude >1 Hz and >50 μV, respectively, continued for >30 min. And in patients with a suppression-burst pattern, electrographic status epilepticus was diagnosed when repetitive epileptiform discharge with a frequency and amplitude >1 Hz and >50 μV, respectively, occupied >50% of a 30-min period [7].

1.3 Results

Sixty-five patients were eligible for the study. The median age was 63, 86% were male, 66% had an initial shockable rhythm, and 88% underwent coronary angiography after admission. Median arrest time was 24 min, median time from ROSC to the start of aEEG monitoring was 5.7 h, and median monitoring period was 53 h. Among these patients, 22 patients (44%) had a good neurological outcome (Table 1.1).

Status epilepticus was recognized in seven patients (11%). Backgrounds and clinical characteristics of patients with status epilepticus were not significantly different from those without status epilepticus (Table 1.1). CNV, flat, and burst suppression patterns led to status epilepticus in one, one, and three patients, respectively. Two patients showed status epilepticus at the start of monitoring. Among these patients, one patient had a good neurological outcome at hospital discharge.

Patients with good and poor neurological outcomes had different clinical characteristics. Patients with a good neurological outcome had shorter arrest times compared with those with a poor outcome and had an initial shockable rhythm. He recovered CNV before status epilepticus. Conversely, six patients with poor prognosis exhibited noncontinuous patterns, such as burst suppression and flat patterns, before status epilepticus, or exhibited status epilepticus at the start of monitoring. Among them, status epilepticus began during hypothermia, with a median time of 18 h after ROSC (Table 1.2).

Table 1.1 Patient's characteristics and neurological outcome

	All patients $n = 65$	Without status epilepticus $n = 58$ (89%)	With status epilepticus $n = 7$ (11%)	p
Age	63 (46–70)	63 (46–70)	70 (63–0)	0.4
Male, no. (%)	56 (86%)	49 (85%)	7 (100%)	0.58
Initial shockable rhythm, no. (%)	43 (66%)	38 (66.7%)	5 (71.4%)	0.69
Arrest time (min)	24 (18–39)	25 (18–40)	23 (20–30)	0.6
Coronary angiography, no. (%)	57 (88%)	51 (88%)	6 (86%)	0.6
Duration from ROSC to the start of aEEG monitoring (h)	5.7 (4.4–8.4)	5.6 (4.4–8.5)	5.9 (4–9.4)	1
Duration of aEEG monitoring (h)	53 (45–66)	53 (46–65)	52 (46–65)	0.91
CPC at hospital discharge				
CPC 1 and 2	27 (42%)	26 (45%)	1 (14%)	0.23
CPC 3 and 4	15 (23%)	11 (19%)	4 (57%)	
CPC 5	23 (35%)	21 (36%)	2 (28%)	

ROSC return of spontaneous circulation; *aEEG* amplitude-integrated electroencephalography; *CPC* cerebral performance categories

Table 1.2 Characteristics and neurological outcome of patients with status epilepticus

	Noncontinuous background $n = 6$	Continuous background $n = 1$
Age	70 (59–71)	59
Male	6/6	1
Arrest time (min)	27 (18–32)	18
Initial shockable rhythm	4/6	1
Duration from ROSC to status epilepticus (h)	18.4 (12.9–29.6)	44.3
Head CT		
Loss of gray white matter contrast	4/6	0
Neurological outcome		
CPC 1 and 2	0/6	1
CPC 3, 4, and 5	6/6	0

ROSC return of spontaneous circulation; *CPC* cerebral performance categories

Here, we present a more detailed clinical course of patients with good neurological outcomes. A 59-year-old man suffered from sudden cardiac arrest and received bystander cardiopulmonary resuscitation. He revealed a ventricular fibrillation when paramedics arrived at the scene. ROSC was achieved 22 min after collapse. Coronary angiography was performed after the admission to our center, and a diagnosis of vasospastic angina was given. He underwent TTM, and aEEG monitoring began 3 h after ROSC. He revealed LV at the start of aEEG monitoring; however, the amplitude developed gradually and CNV was recovered 23 h after ROSC. He was maintained at 34 °C for 24 h and then rewarmed. Midazolam was discontinued after his temperature reached 36 °C. Following this, he exhibited status epilepticus 44 h after ROSC; however, he received no anticonvulsant treatment. He regained consciousness approximately 96 h after ROSC, with a CPC score of 2 at hospital discharge.

1.4 Discussion

The frequency of status epilepticus in comatose post-cardiac-arrest care patients is approximately 10–30% [13–15]. In addition, epileptiform activity, such as electrographic seizures or interictal epileptiform discharges, is recognized in approximately 40% of patients [15]. The status epilepticus in the post-cardiac-arrest period is associated with poor neurological outcomes [13–16]. However, a small number of patients who reveal status epilepticus after ROSC have good neurological outcomes. Legriel et al. reported that 2 of 31 patients with status epilepticus (6%) during post-cardiac-arrest care had a CPC score of 1 or 2 at 1 year after cardiac arrest. These two patients demonstrated background reactivity to stimuli. Legriel et al. discussed that the prognosis of hypoxic encephalopathy with status epilepticus might be improved compared to that in the era before hypothermia treatment, and therapeutic

hypothermia and sedatives with anticonvulsant effects might be beneficial in treating status epilepticus in these post-cardiac-arrest patients [14]. Rundgren et al. categorized patients with status epilepticus into two groups in their study to evaluate the efficacy of aEEG in comatose post-cardiac-arrest patients. The electrographic status epilepticus was recognized in 26 of 95 patients (27%). Of these patients, 16 developed electrographic status epilepticus from a suppression burst, and 10 patients developed electrographic status epilepticus after they revealed a continuous pattern in aEEG. A group of patients with a suppression-burst pattern developed status epilepticus at a relatively early phase during hypothermia. None of these 16 patients regained consciousness. Conversely, two patients who exhibited a continuous pattern regained consciousness. Electrographic status epilepticus occurred after rewarming in these two patients. One of these patients received no anticonvulsant treatment other than propofol for sedation, and he recovered to CPC 2. Another patient was administered midazolam, fosphenytoin, diazepam, and topiramate. She recovered to CPC 3 after 6 months. This study shows that the continuous pattern of background activity before status epilepticus is a key factor to obtaining a good neurological outcome. This was consistent with the results of our study. It is important to understand the process of status epilepticus development (Figs. 1.5 and 1.6). For this reason, cEEG monitoring from an early phase after ROSC is necessary. Furthermore, aEEG with reduced montage could play an important role in providing information on background activity changes. Intensivists and emergency physicians could understand this process at the bedside. This could lead to prompt anticonvulsant therapy for patients with the potential for good neurological recovery.

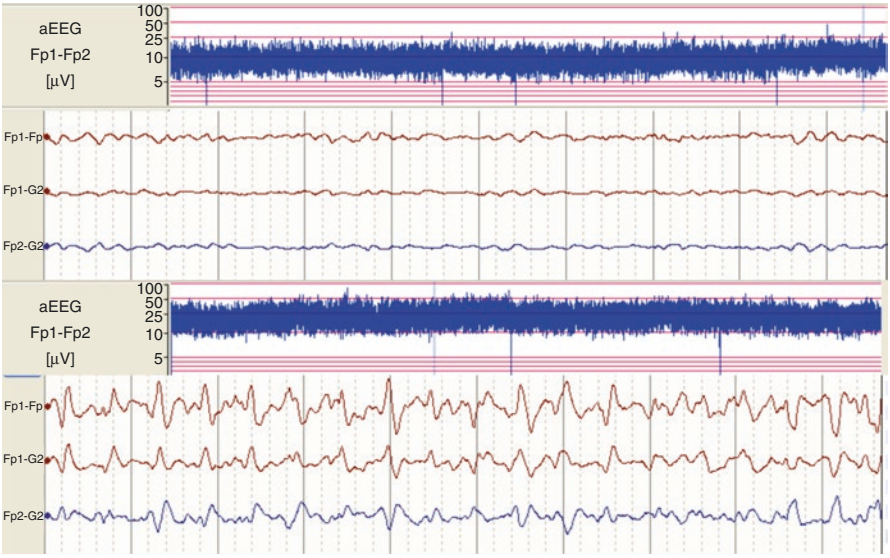


Fig. 1.5 Status epilepticus developed from a continuous normal voltage trace

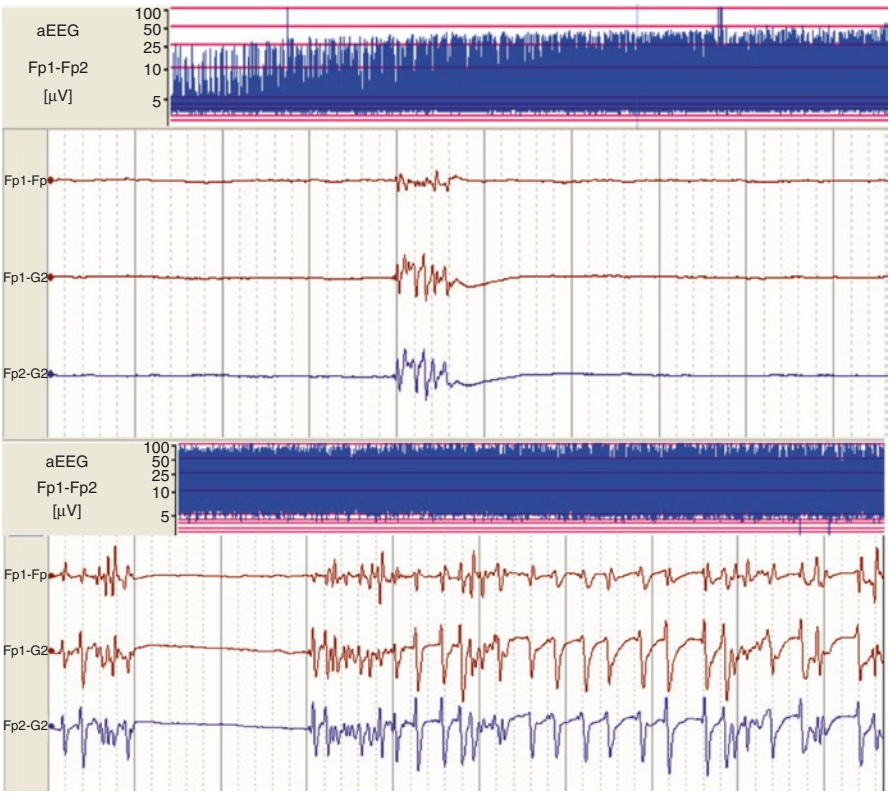


Fig. 1.6 Status epilepticus developed from a burst suppression trace

Frieberg et al. mentioned in their clinical review that "A major question, yet to be answered, is whether post-anoxic ESE is a condition that causes further brain injury, or is simply a sign of the hypoxic-ischemic encephalopathy" [17].

Current guidelines recommend anticonvulsant therapy for seizures after cardiac arrest, which is based on evidence that anticonvulsant therapy is recommended to prevent damage of the brain caused by prolonged status epilepticus. Seizures may increase the cerebral metabolic rate and exacerbate brain injury caused by cardiac arrest. However there has been no definite evidence to recommend anticonvulsant therapy vs no treatment in status epilepticus among post-cardiac-arrest patients. As mentioned above, one patient in the study by Rundgren et al. had a good neurological outcome without aggressive anticonvulsant therapy for status epilepticus. In addition, one patient who developed electrographic status epilepticus after rewarming and cessation of midazolam had a CPC score of 2 at hospital discharge without anticonvulsant therapy in our study. It remains uncertain whether he might have developed better cerebral function if he were treated aggressively with anticonvulsant therapy.

Status epilepticus in post-cardiac-arrest patients is often refractory; therefore, aggressive anticonvulsant therapies, such as large amounts of anesthetic agents like midazolam, propofol, or barbiturates, are required to control electrographic seizure activity. It is difficult to decide whether these kinds of anesthetic agents should be used in each situation. The sedative effects of these drugs lead to difficulties in early prognostication and more complicated post-cardiac arrest care. Patients sedated with barbiturates usually need a long period before regaining consciousness. Furthermore, deep sedation caused by these agents may lead to various complications, such as circulatory collapse; severe nosocomial infections, like pneumonia; ICU-acquired weakness; and deep vein thrombosis. These complications may be detrimental for the prognosis of post-cardiac-arrest patients.

A multicenter randomized controlled trial, "TELSTAR," is recruiting participants. This study recruits comatose post-cardiac-arrest patients who are admitted to ICUs, monitored with cEEG, and report electrographic status epilepticus after ROSC. Patients are randomly assigned to aggressive anticonvulsant therapy to suppress all seizure activity or no treatment. The aggressive therapy includes both antiepileptic and anesthetic drugs, like thiopental. The primary outcome is neurological outcome at 3 months after cardiac arrest [18].

This study is recruiting all patients with status epilepticus and is not considering the background activity before status epilepticus. The frequency of patients with the potential for recovery, i.e., patients with status epilepticus from a continuous background, is very small. We argue that over half of the patients with status epilepticus exhibit burst suppression or noncontinuous patterns as background activity, and these patients usually have very severe brain damage with a poor prognosis. If these patients are included in the study, anticonvulsant treatment might not show any benefit.

We suggest that the efficacy of anticonvulsant treatment should be evaluated only in patients who exhibit continuous background aEEG patterns before status epilepticus. However, these patients would be a relatively small population within the population of patients with hypoxic encephalopathy.

In addition, the role of aEEG in this field is challenging. cEEG with standard montage is the gold standard to detect nonconvulsive status epilepticus. In some specialized centers, cEEG recordings are sent to neurophysiologists online and interpreted continuously. However, most centers do not have these sophisticated systems, and recordings are interpreted by experts on a daily basis. This causes delays in diagnosis and therapeutic intervention; therefore, the detection of status epilepticus with monitoring of trends in quantitative EEG by non-neurologists is desired.

qEEG is a visual representation of statistically transformed raw EEG signals. Although aEEG is a representative method, other qEEGs have been used to detect seizure activity. The compressed spectral array is another common method, which consists of a color display representing power in different frequency bands. Other qEEG methods include techniques that display EEG data based on rhythmicity or spectral symmetry.

Seizure activity causes an abrupt elevation of lower and upper margin of the band when monitoring aEEG. There are several studies that examined the efficacy of

aEEG monitoring to detect electrographic seizure activity; however, the results of these studies are not optimistic.

In neonates, aEEG is used to detect seizure activity and monitoring cerebral activity in various encephalopathies. aEEG monitoring can help detect clinical and nonclinical seizures; however, its sensitivity and specificity have been as insufficient when compared with conventional cEEG. Rakshabhuvankar et al. conducted a systematic review that included 10 studies and 433 patients. These studies compared the simultaneous recording of aEEG and cEEG. The sensitivity and specificity for individual seizure detection were 76% and 85%, respectively, for aEEG with a raw trace, and 39% and 95%, respectively, for aEEG without a raw trace. They concluded that aEEG has a relatively low and variable sensitivity for seizure detection and cannot be recommended as the sole method for the management of neonatal seizures [19].

A few small single-center studies have evaluated the efficacy of aEEG for seizure detection in the management of seizures in adult patients. Nitzschke et al. examined whether aEEG recordings derived from a frontal single-channel EEG could detect seizures compared with raw EEG recordings. The sensitivity and specificity of aEEG were 40% and 89%, respectively. In this study, aEEG was evaluated by intensive care physicians who received training in aEEG interpretation [19]. Another study by Dericioglu et al. examined the ability of nonexpert ICU physicians and nurses to detect seizures. In this study, raw EEG recordings were converted to aEEG and density spectral array (DSA), and raters interpreted the recordings of aEEG and DSA without the raw trace. They found that the sensitivity and specificity for seizure detection were high and inter-rater reliability was acceptable. In addition, there was no difference between physician and nurses, and they concluded that ICU fellows and residents can achieve acceptable levels of accuracy for seizure identification using the digital EEG trend analysis methods following brief training [20].

Considering these results, aEEG cannot substitute cEEG in monitoring seizures. Today's gold standard for monitoring nonclinical or nonconvulsive seizures is cEEG. However, aEEG should play a complementary role to cEEG. In addition, we should not interpret aEEG recordings without the raw trace. For a non-neurologist, aEEG traces suggesting seizure activity should warrant a consultation to the neurologist. Nonetheless, aEEG could help non-neurologists by assisting with continuous monitoring and timely interventions of seizure.

Another problem with seizure monitoring in critical care settings is whether the reduced montage number of channel leads is acceptable for seizure management. The conventional 10–20 system montage with full leads is a standard technique to detect seizure. This montage usually requires specially trained EEG technicians, which are not available 24 h a day and 7 days a week in most centers. Furthermore, the placement of many electrodes is time-consuming, and frequent care for patients in ICU is a major obstacle for the placement of many electrodes. Patients may need to be moved frequently, and typically these patients have many lines or drains. Several studies have evaluated the efficacy of a reduced electrode montage in seizure detection. These studies report relatively low sensitivity (approximately 70%) and high specificity (approximately 90%) of this method for seizure detec-

tion [21–25]. Most studies used a reduced montage with 7–8 leads; however, some studies examined the efficacy of subhairline leads. Subhairline leads have advantage of easy placement because hydrogel electrodes can be used in a similar manner to that in electrocardiography. Brenner et al. examined the efficacy of subhairline leads in patients who exhibited altered mental states after seizure in the emergency department. A neurophysiologist could diagnose nonconvulsive status epilepticus in all 12 patients using the subhairline montage compared with the standard 10–20 system [26].

These studies included patients with various backgrounds and clinical conditions. Vanherpe et al. examined the efficacy of the subhairline or eight-lead montage in comatose post-cardiac-arrest patients treated with TTM. They categorized the EEG recordings into three categories: without ictal activity, with interictal activity, and with probable electrographic seizure. The sensitivity for detecting probable electrographic seizure was 92% and 100% for hairline and eight-lead montage, respectively. Vanherpe et al. discussed that global seizures are more common in hypoxic encephalopathy compared with other conditions; therefore, the sensitivity of hairline and eight-lead montage is more acceptable in these populations [27].

In our study, 11% of patients revealed status epilepticus. This fits with the low number reported in previous studies. We used a single bipolar frontal hairline lead in our study. Considering the results of these studies, this method might not have enough sensitivity to detect all patients with status epilepticus. We decided to use this method as the simplest way without obstacles to introduce aEEG in our center. Therefore, ease and simplicity were most highly valued. Our main purpose was to use aEEG as a guide in prognosis. We argue that we will use a montage with more leads to detect seizures with a greater sensitivity. During the very early phase after ROSC, it is difficult to place many leads; however, after a few hours post-ROSC, we could place an additional five or six leads.

The diagnostic criteria of EEG for nonconvulsive status epilepticus are generally defined as definite, if the following conditions are recognized [28]:

1. Focal or generalized spikes, sharp waves, or sharp-and-slow complexes at frequencies of >2.5 Hz
2. Focal or generalized spikes, sharp waves, or sharp-and-slow complexes at frequencies ≤2.5 Hz or rhythmic activity >0.5 Hz and one of the following:
   - Electrographic and clinical improvement after an IV trial of an antiseizure drug
   - Subtle clinical ictal phenomena during the EEG pattern
   - Typical spatiotemporal evolution

These criteria should be met during at least 10 consecutive seconds, and abnormal EEG should constitute >50% of the monitoring period.

The diagnostic criteria of aEEG to diagnose electronic status epilepticus have not been developed. Rundgren et al. diagnosed electrographic status epilepticus in their study based on the pattern of aEEG and simultaneous raw EEG recordings, and we used these criteria in our study. They applied different criteria to the electrographic

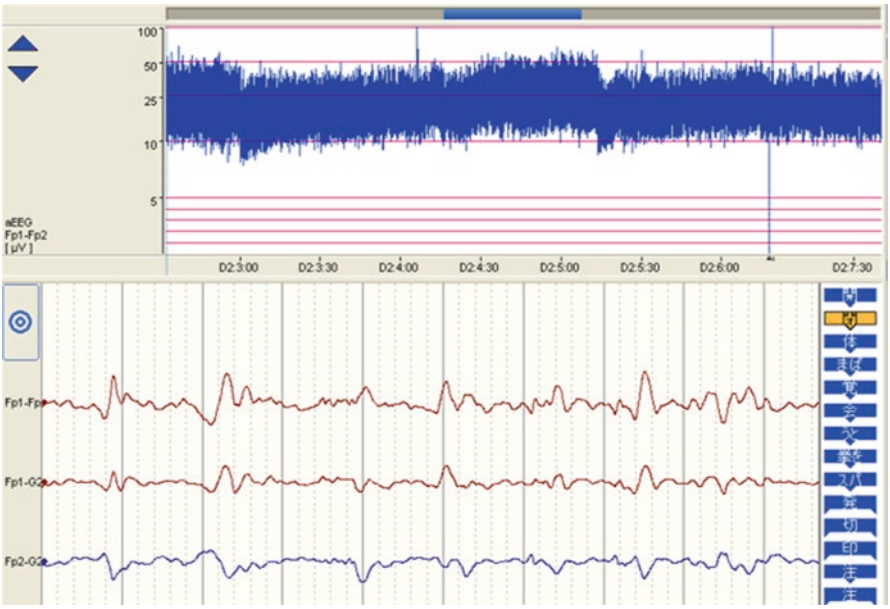


Fig. 1.7 Periodic discharges are recognized in the raw trace. This aEEG trace meets the criteria of continuous normal voltage

status epilepticus, from continuous pattern and suppression burst. In patients with a continuous pattern before status epilepticus, electrographic status epilepticus was diagnosed when the repetitive epileptiform discharge with a frequency > 1 Hz and amplitude >50 μV continued for more than 30 min and in patients with a suppression-burst pattern, when the repetitive epileptiform discharge with a frequency and amplitude of >1 Hz and >50 μV, respectively, occupies more than 50% of a 30-min period [7]. These criteria are different from the current gold standard because of the time of publication of their study. The incidence of status epilepticus is strongly affected by diagnostic criteria; therefore, while aEEG is a complementary technique to detect seizures, the actual diagnosis of seizure requires the use of the raw cEEG trace, and standard diagnostic criteria should be referenced.

Periodic discharges are often recognized during ictal or interictal periods in post-cardiac-arrest patients. aEEG may have a limited ability to detect the periodic discharges. When seizures start, the lower and upper margin of the band of the aEEG trace elevates suddenly. However, periodic low-frequency discharge might not show remarkable changes on an aEEG trace. The upper margin of the band may increase; however, this change may be difficult to notice when periodic discharges continue for long periods (Fig. 1.7). These aEEG traces, with periodic discharges, might be recorded as continuous normal voltage or continuous pattern traces. Periodic discharges have been reported to be associated with poor outcome in some studies [28]; therefore, we should pay attention to periodic discharges when using aEEG in prognostication.

1.5 Conclusion (Perspective from Our Study)

Our study showed that aEEG can help to identify patients with status epilepticus with limited sensitivity and provide important information regarding background activity before status epilepticus. This may lead to a better prognostication of patients with status epilepticus and aid to determine an indication for aggressive anticonvulsant therapy for each patient. With this aim, we have to begin aEEG monitoring from the early phase after ROSC.

The sensitivity of aEEG with a single frontal lead alone is not sufficient. Additional leads should be placed once patients have been stabilized to detect seizure activity. The efficacy of anticonvulsant therapy in post-cardiac-arrest patients with status epilepticus remains unknown. We believe that patients with a continuous background trace before status epilepticus should be treated aggressively.

References

1. Westhall E, Rossetti AO, van Rootselaar A-F, Wesenberg Kjaer T, Horn J, Ullén S, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology. 2016;86(16):1482–90. https://doi.org/10.1212/WNL.0000000000002462.
2. Lamartine Monteiro M, Taccone FS, Depondt C, Lamanna I, Gaspard N, Ligot N, et al. The prognostic value of 48-h continuous EEG during therapeutic hypothermia after cardiac arrest. Neurocrit Care. 2016;24(2):153–62. https://doi.org/10.1007/s12028-015-0215-9.
3. Spalletti M, Carrai R, Scarpino M, Cossu C, Ammannati A, Ciapetti M, et al. Single electroencephalographic patterns as specific and time-dependent indicators of good and poor outcome after cardiac arrest. Clin Neurophysiol. 2016;127(7):2610–7. https://doi.org/10.1016/j.clinph.2016.04.008.
4. Tjepkema-Cloostermans MC, Hofmeijer J, Trof RJ, Blans MJ, Beishuizen A, van Putten MJAM. Electroencephalogram predicts outcome in patients with postanoxic coma during mild therapeutic hypothermia. Crit Care Med. 2015;43(1):159–67. https://doi.org/10.1097/CCM.0000000000000626.
5. Hellström-westas L. Amplitude-integrated EEG classification and interpretation in preterm and term infants. NeoReviews. 2006;7(2):76–97.
6. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005;365(9460):663–70. https://doi.org/10.1016/S0140-6736(05)17946-X.
7. Rundgren M, Westhall E, Cronberg T, Rosén I, Friberg H. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med. 2010;38(9):1838–44. https://doi.org/10.1097/CCM.0b013e3181eaa1e7.
8. Oh SH, Park KN, Kim YM, Kim HJ, Youn CS, Kim SH, et al. The prognostic value of continuous amplitude-integrated electroencephalogram applied immediately after return of spontaneous circulation in therapeutic hypothermia-treated cardiac arrest patients. Resuscitation. 2013;84(2):200–5. https://doi.org/10.1016/j.resuscitation.2012.09.031.
9. Thoresen M, Hellstrom-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010;126(1):e131–9. https://doi.org/10.1542/peds.2009-2938.

10. Oh SH, Park KN, Shon YM, Kim YM, Kim HJ, Youn CS, et al. Continuous amplitude-integrated electroencephalographic monitoring is a useful prognostic tool for hypothermia-treated cardiac arrest patients. Circulation. 2015;132(12):1094–103. https://doi.org/10.1161/CIRCULATIONAHA.115.015754.
11. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for post-resuscitation care 2015: section 5 of the European resuscitation council guidelines for resuscitation. Resuscitation. 2015;95:202–22. https://doi.org/10.1016/j.resuscitation.2015.07.018.
12. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: post–cardiac arrest care. Circulation. 2015;132(18 suppl 2):S465–82. https://doi.org/10.1161/CIR.0000000000000262.
13. Rittenberger JC, Popescu A, Brenner RP, Guyette FX, Callaway CW. Frequency and timing of nonconvulsive status epilepticus in comatose post-cardiac arrest subjects treated with hypothermia. Neurocrit Care. 2012;16(1):114–22. https://doi.org/10.1007/s12028-011-9565-0.
14. Legriel S, Hilly-Ginoux J, Resche-Rigon M, Merceron S, Pinoteau J, Henry-Lagarrigue M, et al. Prognostic value of electrographic postanoxic status epilepticus in comatose cardiac-arrest survivors in the therapeutic hypothermia era. Resuscitation. 2013;84(3):343–50. https://doi.org/10.1016/j.resuscitation.2012.11.001.
15. Mani R, Schmitt SE, Mazer M, Putt ME, Gaieski DF. The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. Resuscitation. 2012;83(7):840–7. https://doi.org/10.1016/j.resuscitation.2012.02.015.
16. Rossetti AO, Logroscino G, Liaudet L, Ruffieux C, Ribordy V, Schaller MD, et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. Neurology. 2007;69(3):255–60. https://doi.org/10.1212/01.wnl.0000265819.36639.e0.
17. Friberg H, Westhall E, Rosén I, Rundgren M, Nielsen N, Cronberg T. Clinical review: continuous and simplified electroencephalography to monitor brain recovery after cardiac arrest. Crit Care. 2013;17(4):233. https://doi.org/10.1186/cc12699.
18. Ruijter BJ, Van Putten MJ, Horn J, Blans MJ, Beishuizen A, Van Rootselaar A-F, et al. Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR): study protocol for a randomized controlled trial. Trials. 2014;6(15):433. https://doi.org/10.1186/1745-6215-15-433.
19. Nitzschke R, Müller J, Engelhardt R, Schmidt GN. Single-channel amplitude integrated EEG recording for the identification of epileptic seizures by nonexpert physicians in the adult acute care setting. J Clin Monit Comput. 2011;25(5):329–37. https://doi.org/10.1007/s10877-011-9312-2.
20. Dericioglu N, Yetim E, Bas DF, Bilgen N, Caglar G, Arsava EM, et al. Non-expert use of quantitative EEG displays for seizure identification in the adult neuro-intensive care unit. Epilepsy Res. 2015;109:48–56. https://doi.org/10.1016/j.eplepsyres.2014.10.013.
21. Rubin MN, Jeffery OJ, Fugate JE, Britton JW, Cascino GD, Worrell GA, et al. Efficacy of a reduced electroencephalography electrode array for detection of seizures. Neurohospitalist. 2014;4(1):6–8. https://doi.org/10.1177/1941874413507930.
22. Ma BB, Johnson EL, Ritzl EK. Sensitivity of a reduced EEG montage for seizure detection in the neurocritical care setting. J Clin Neurophysiol. 2018;1:256. https://doi.org/10.1097/WNP.0000000000000463.
23. Karakis I, Montouris GD, Otis JAD, Douglass LM, Jonas R, Velez-Ruiz N, et al. A quick and reliable EEG montage for the detection of seizures in the critical care setting. J Clin Neurophysiol. 2010;27(2):100–5. https://doi.org/10.1097/WNP.0b013e3181d649e4.
24. Kolls BJ, Husain AM. Assessment of hairline EEG as a screening tool for nonconvulsive status epilepticus. Epilepsia. 2007;48(5):959–65. https://doi.org/10.1111/j.1528-1167.2007.01078.x.
25. Young GB, Sharpe MD, Savard M, Al Thenayan E, Norton L, Davies-Schinkel C. Seizure detection with a commercially available bedside EEG monitor and the subhairline montage. Neurocrit Care. 2009;11(3):411–6. https://doi.org/10.1007/s12028-009-9248-2.

26. Brenner JM, Kent P, Wojcik SM, Grant W. Rapid diagnosis of nonconvulsive status epilepticus using reduced-lead electroencephalography. West J Emerg Med. 2015;16(3):442–6. https://doi.org/10.5811/westjem.2015.3.24137.
27. Vanherpe P, Schrooten M. Minimal EEG montage with high yield for the detection of status epilepticus in the setting of postanoxic brain damage. Acta Neurol Belg. 2017;117(1):145–52. https://doi.org/10.1007/s13760-016-0663-9.
28. Leitinger M, Beniczky S, Rohracher A, Gardella E, Kalss G, Qerama E, et al. Salzburg consensus criteria for non-convulsive status epilepticus—approach to clinical application. Epilepsy Behav. 2015;49:158–63. https://doi.org/10.1016/j.yebeh.2015.05.007.

Chapter 2
Comparison of Neurological Outcome Between the Primary Percutaneous Coronary Intervention-First and Targeted Temperature Management-First Strategies in Out-of-Hospital Cardiac Arrest Patients: J-PULSE-Hypo Registry

Hayato Hosoda and Yoshio Tahara

Abstract Target temperature management (TTM) improves neurological outcome in out-of-hospital cardiac arrest (OHCA) patients. TTM should be performed for OHCA patients as soon as possible. On the other hand, we also need to perform emergency coronary angiography and primary percutaneous coronary intervention (PCI) against ongoing myocardial ischemia for the patient after cardiac arrest of cardiac etiology. However, there have been few studies showing which therapy should be done first. We evaluate the priority of TTM or PCI after return of spontaneous circulation (ROSC) in OHCA patients using the data of the J-PULSE-Hypo Registry. This registry consisted of 14 institutes and retrospectively collected the patient after cardiac arrest to study the effect of TTM. These patients were divided into the PCI-first group and the TTM-first group to compare neurological outcomes. A favorable outcome was defined as a cerebral performance category (CPC) of 1–2. A total of 195 patients after cardiac arrest of cardiac etiology were enrolled in this present study. All patients underwent both PCI and TTM. There were no significant differences between the PCI-first group ($n = 95$) and the TTM-first group ($n = 100$) in the clinical characteristics. The PCI-first group had a longer median interval from collapse to achieve target core temperature (PCI-first, 330 [203–467] min vs. TTM-first, 179 [80–295] min; $P < 0.01$) than the TTM-first group. There were no significant differences in the rate of favorable outcome at 30 days (PCI-first, 54% vs.

H. Hosoda (✉) · Y. Tahara
National Cerebral and Cardiovascular Center, Osaka, Japan

M. Aibiki, S. Yamashita (eds.), *A Perspective on Post-Cardiac Arrest Syndrome*,
https://doi.org/10.1007/978-981-13-1099-7_2

TTM-first, 50%; $P = 0.67$) between the two groups. The present multicenter registry study indicates that the timing of PCI did not significantly affect neurological outcome and survival in OHCA patients although PCI-first strategy delayed the induction of TTM.

Keywords Target temperature management · Out-of-hospital cardiac arrest · Percutaneous coronary intervention

Abbreviations

ACS	Acute coronary syndrome
CA	Cardiac arrest
CAG	Coronary angiography
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
IABP	Intra-aortic balloon pumping
LVEF	Left ventricular ejection fraction
OHCA	Out-of-hospital cardiac arrest
PCAS	Post-cardiac arrest syndrome
PCI	Percutaneous coronary intervention
PCPS	Percutaneous cardiopulmonary support
ROSC	Return of spontaneous circulation
TTM	Target temperature management

2.1 Introduction

Target temperature management (TTM) improves neurological outcome in out-of-hospital cardiac arrest (OHCA) patients [1–3]. It is noted that TTM should be performed for OHCA patients as soon as possible [4]. On the other hand, we also need to perform emergency coronary angiography and primary percutaneous coronary intervention (PCI) against ongoing myocardial ischemia for the patient after cardiac arrest of cardiac etiology since hospital care consisting of PCI and TTM improves survival with good neurological recovery in such patients [5, 6]. However, there have been few studies showing which therapy should be done first.

The present study aimed to examine the priority of TTM or PCI after return of spontaneous circulation (ROSC) in patients with OHCA, using the data of the J-PULSE-Hypo registry [7].

2.2 Methods

2.2.1 Patients

The present study was conducted using data from the J-PULSE-Hypo registry, which was a prospective, multicenter, cohort study of post-cardiac arrest syndrome (PCAS) patients who received TTM at 14 institutes (Fig. 2.1). Patients were registered between January 2005 and March 2011. Four hundred fifty-two consecutive comatose patients who were treated with TTM after return of spontaneous circulation (ROSC) after OHCA were enrolled in this registry when they met the following criteria: (1) patients aged ≥18 years; (2) stable hemodynamics after ROSC, including stabilization by drugs or assisted circulation, such as intra-aortic balloon pumping (IABP) or percutaneous cardiopulmonary support (PCPS); (3) persistent coma (Glasgow Coma Scale ≤ 8) after ROSC; and (4) presumed cardiac etiology of cardiac arrest according to the Utstein Style guidelines [8]. Patients were excluded for the following reasons: pregnancy, aortic dissection, pulmonary embolism, drug addiction, and poor daily activity before the onset of cardiac arrest. In addition, we selected patients who were diagnosed with acute coronary syndrome (ACS) and underwent both PCI and TTM after ROSC. Patients performed PCI after finishing TTM were excluded. We divided these patients into two groups, the PCI-first group and the TTM-first group. The PCI-first group was defined as that we performed PCI before induction of TTM, whereas the TTM-first group was defined as that we introduced TTM before PCI. The study was conducted in accordance with the ethical guidelines for epidemiological studies and was approved by the ethics committee of the National Cerebral and Cardiovascular Center. Ethical review boards at all 14 participating centers approved the study protocol.

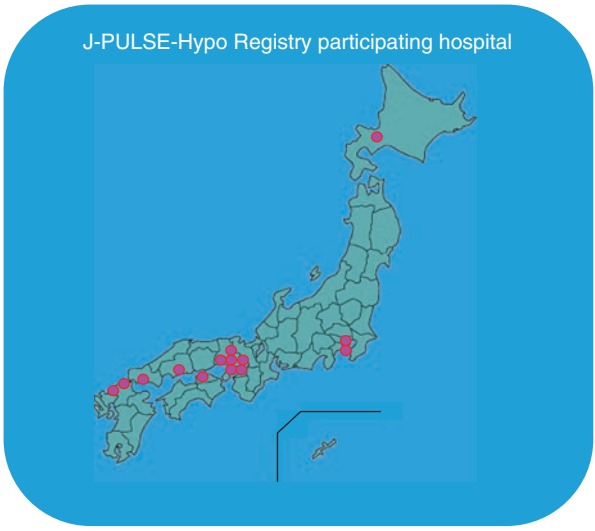


Fig. 2.1 Geographic location of the 14 participating hospitals

2.2.2 Treatment

Patients were received standard cardiopulmonary resuscitation (CPR) and PCAS care according to the 2005 American Heart Association guidelines [9]. TTM was performed with sedation and analgesia according to the hospital's established procedures. If hemodynamic instability persisted after ROSC, despite adequate fluid resuscitation and intravenous infusion of vasopressors and inotropes, IABP and/or PCPS was performed as appropriate. TTM was performed with the use of noninvasive cooling with surface cooling and/or invasive cooling with blood cooling at the discretion of the sites. Core temperature was immediately monitored by the bladder or rectal temperature on hospital admission and during the TTM. A target core temperature of 32–35 °C was maintained for 12–72 h. Rewarming was conducted gradually and took at least 24–72 h. Emergency coronary angiography (CAG) was performed if acute coronary syndrome (ACS) was suspected, and percutaneous coronary intervention (PCI) was performed if it is necessary.

2.2.3 Data Collection

Data were collected according to the Utstein Style guidelines using software designed exclusively for the J-PULSE-Hypo study registry [7, 8]. Data were accumulated and registered by each facility. The following parameters were recorded for each study subject: age, sex, presence of bystander CPR, initial rhythm, time from collapse to ROSC, mechanical circulation support after ROSC, etiology of cardiac arrest, timing of CAG and PCI, cooling method and duration, rewarming duration, and neurological outcome.

2.2.4 Study Outcomes

Outcome data included survival at 90 days and favorable neurological outcome until 90 days after CA. The survival and favorable neurological outcome was compared between the two groups for all patients and for specified subgroups of patients. We assessed subgroups defined by the location of coronary artery stenosis and left ventricular ejection fraction (LVEF). The patient's neurological outcome was assessed using the Glasgow-Pittsburgh cerebral performance category (CPC). Favorable neurological outcome was defined as CPC 1 (good recovery) or CPC 2 (moderate disability) on a five-category scale. The other categories were CPC 3 (severe disability), CPC 4 (vegetative state), and CPC 5 (death) [8].

2.2.5 *Statistical Analysis*

Study patients were divided into two groups based on the timing of PCI or TTM (PCI-first group and TTM-first group). We used *t*-test or Mann-Whitney *U* test to compare the averages of continuous variables and chi-square tests to compare the proportion of categorical variables between groups as appropriate. Variables that approximate a normal distribution were summarized as mean (standard deviation) and groups compared using *t*-tests. Other continuous or ordinally scaled variables were summarized as median ± interquartile range and group compared using Mann-Whitney *U* test. Survival curves were drawn by the Kaplan-Meier method and were compared with the log-rank test. All analyses were conducted using JMP version 12 (SAS Japan, Tokyo, Japan). *P*-values less than 0.05 were considered statistically significant.

2.3 Results

During the study period, 452 comatose adult patients treated with post-ROSC cooling were enrolled in the J-PULSE-Hypo study registry. Among these patients, 283 of 452 patients were diagnosed with acute coronary syndrome. One hundred ninety-five of 283 patients underwent both PCI and CAG. Finally, 195 patients were investigated in this study. These ACS patients were divided into two groups based on the timing of TTM and PCI (95 [49%] cases in the PCI-first group, 100 [51%] cases in the TTM-first group) (Fig. 2.2). Table 2.1 showed the baseline characteristics of the study patients. Overall, the median age was 62 years, and patients were predominantly male (88%). Fifty-two % of the patients were received bystander CPR and 76% presented with an initial shockable rhythm (VF or pulseless VT). Median time from arrest to ROSC was 23 min. There were no significant differences between the two groups with regard to having witnessed cardiac arrest, bystander CPR status, and initial cardiac rhythm. The median time from collapse to ROSC and collapse to hospital arrival was comparable between the two groups. Table 2.2 showed characteristics and time interval of TTM between the two groups. The median time interval from collapse to target core temperature and from ROSC to target core temperature was significantly longer in TTM-first group than in PCI-first group although the median time interval from induction of TTM to target core temperature was comparable between the two groups. Angiographic finding and the usage of IABP or PCPS were no significant differences between the two groups (Table 2.3).

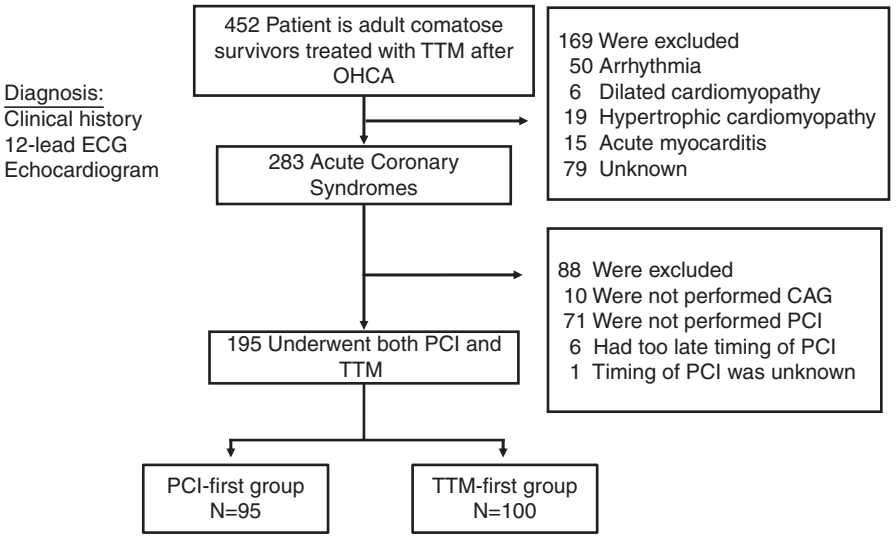


Fig. 2.2 The study flow diagram

Table 2.1 Baseline characteristics of the PCI-first group and TTM-first group

	Overall ($N = 195$)	PCI-first group ($N = 95$)	TTM-first group ($N = 100$)	P
Age, year	62 (54–69)	63 (54–69)	62 (55–68)	0.49
Male, *n* (%)	172 (88)	90 (95)	82 (82)	0.0071
Witnessed cardiac arrest, *n* (%)	173 (89)	87 (92)	86 (86)	0.26
Bystander CPR, *n* (%)	101 (52)	54 (56)	47 (47)	0.20
Initial cardiac rhythm, *n* (%)				0.56
VF/pulseless VT	148 (76)	72 (77)	76 (74)	
PEA	15 (8)	5 (5)	10 (10)	
Asystole	10 (5)	6 (6)	4 (4)	
Unidentified rhythm	21 (11)	11 (12)	10 (10)	
ROSC before admission, *n* (%)	108 (55)	54 (57)	54 (54)	0.77
Time interval, min				
Collapse to ROSC	23 (13–40)	23 (13–40)	24 (14–40)	0.97
Collapse to hospital arrival	26 (18–36)	25 (16–37)	26 (18–36)	0.73

Values are *n* (%) or medians (IQR)
CPR cardiopulmonary resuscitation; *PCI* percutaneous coronary intervention; *PEA* pulseless electrical activity; *ROSC* return of spontaneous circulation; *TTM* target temperature management; *VF* ventricular fibrillation; *VT* ventricular tachycardia

Table 2.2 Characteristics and time interval of TTM

	PCI-first group ($N = 95$)	TTM-first group ($N = 100$)	P
Target temperature, °C	34 (34–34)	34 (34–34)	<0.001
Time interval, min			
Collapse to induction of TTM	178 (87–246)	47 (32–64)	<0.001
ROSC to induction of TTM	150 (52–219)	20 (8–48)	<0.001
Hospital arrival to induction of TTM	149 (69–214)	18 (4–37)	<0.001
Collapse to target core temperature	352 (256–504)	184 (101–308)	<0.001
ROSC to target core temperature	330 (203–467)	169 (78–292)	<0.001
Hospital arrival to target core temperature	320 (202–491)	162 (77–286)	<0.001
Induction of TTM to target core temperature	147 (68–300)	135 (49–267)	0.41
Duration of cooling, h	26 (24–47)	24 (24–30)	0.096
Duration of rewarming ≤48, *n* (%)	60 (65)	68 (68)	0.43

Values are *n* (%) or medians (IQR)
PCI percutaneous coronary intervention; *ROSC* return of spontaneous circulation; *TTM* target temperature management

Table 2.3 Angiographic finding and usage of IABP/PCPS

	PCI-first group ($N = 95$)	TTM-first group ($N = 100$)	P
Pre-PCI TIMI flow grade 0 or 1, *n* (%)	75 (81)	76 (76)	0.59
Post-PCI TIMI flow grade 3, *n* (%)	89 (96)	87 (87)	0.067
Multivessel disease, *n* (%)	39 (41)	44 (44)	0.27
1 vessel disease, *n* (%)	56 (59)	56 (56)	
2 vessel disease, *n* (%)	21 (22)	31 (31)	
3 vessel disease, *n* (%)	18 (19)	13 (13)	
IABP usage, *n* (%)	60 (63)	62 (62)	0.88
PCPS usage, *n* (%)	25 (26)	38 (38)	0.093

Values are *n* (%)
IABP intra-aortic balloon pumping; *PCI* percutaneous coronary intervention; *PCPS* percutaneous cardiopulmonary support; *TIMI* thrombolysis in myocardial infarction; *TTM* target temperature management

2.3.1 Outcome

Survival was 71% (68 of 95) for PCI-first group and 72% (72 of 100) for TTM-first group at 90 days (Fig. 2.3). There is no significant difference in survival at 90 days between the two groups. Figure 2.4 showed the frequency of favorable neurological outcome at 30 days (54% [51 of 95] PCI-first group vs. 48% [48 of 100] TTM-first group, $P = 0.47$) and 90 days (52% [49 of 95] vs. 49% [49 of 100], $P = 0.78$,

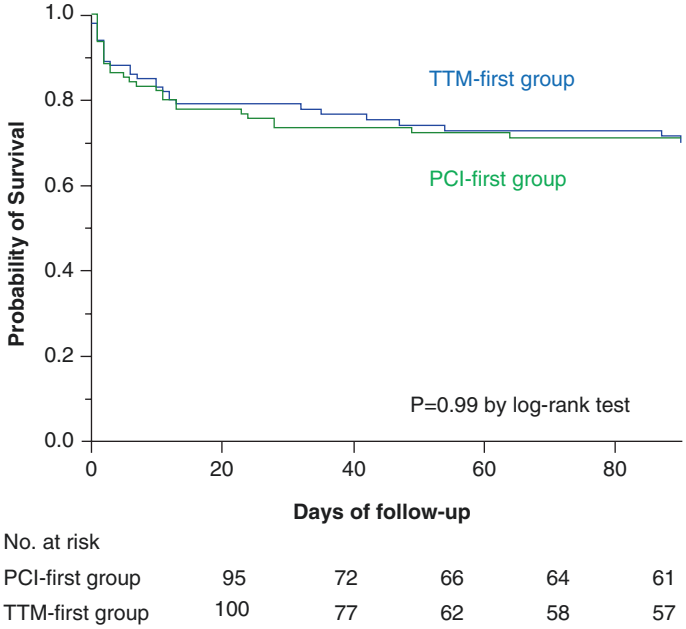
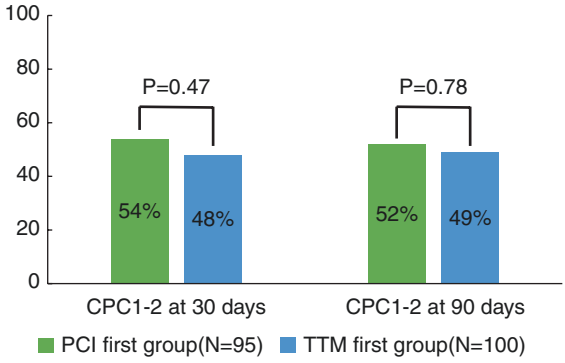


Fig. 2.3 Kaplan-Meier curves of the PCI-first group and TTM-first group for 90 days

Fig. 2.4 The frequency of favorable outcome at 30 and 90 days



respectively). There is no significant difference in the frequency of favorable neurological outcome between the two groups.

Figure 2.5 showed the location of coronary artery stenosis. LMT or LAD lesion was 43% (41 of 95) in PCI-first group and 52% (52 of 100) in TTM-first group. Multivessel disease was 22% and 26%, respectively. Figure 2.6 showed similar results when the patients were classified according to the location of coronary artery stenosis. There was no significant difference in both survival at 90 days and the frequency of favorable outcomes until 90 days between the two groups.

There was no significant difference in both survival and the frequency of favorable outcomes until 90 days in the patients with reduced ventricular ejection fraction (Fig. 2.7).

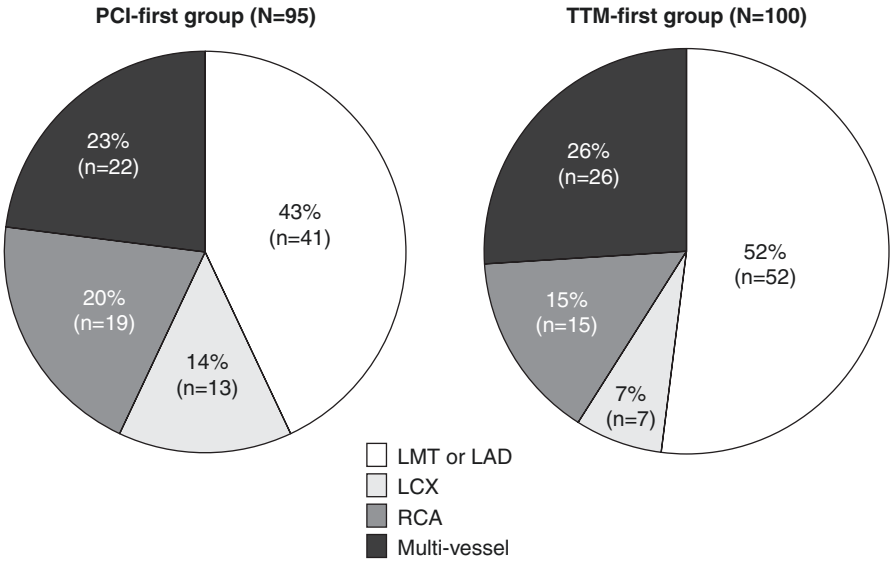


Fig. 2.5 The location of coronary artery stenosis

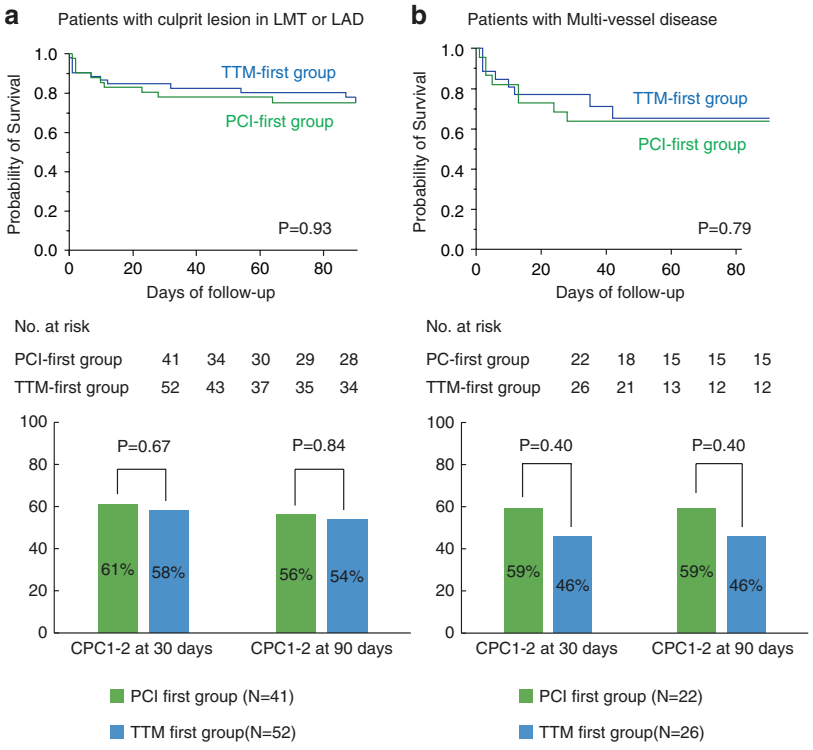


Fig. 2.6 Kaplan-Meier curves at 90 days and the rate of favorable outcome between two groups categorized by culprit lesion

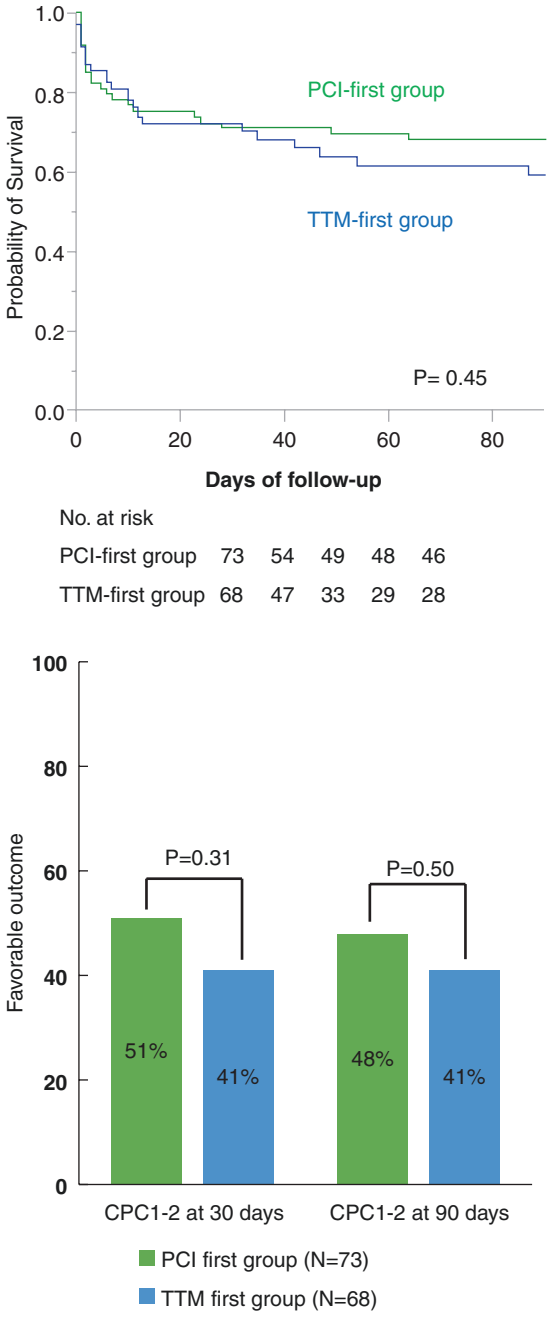


Fig. 2.7 Kaplan-Meier curves at 90 days with reduced ejection fraction (LVEF ≤40)

2.4 Discussion

This study investigated the priority of TTM or PCI after ROSC in the OHCA patients using multicenter registry. The results showed that the sequences of TTM and PCI did not affect the survival and the neurological outcome. On the other hand, the PCI-first group had a longer median interval from CA to target core temperature than the TTM-first group.

Previous studies have shown that both TTM and coronary interventions for the patients following OHCA can positively influence prognosis [10–12]. Therefore, 2015 AHA Guidelines have recommended both TTM and acute coronary interventions [13]. However, few studies investigated which therapy should be done first. The previous prospective observational study reported whether TTM or CAG was performed earlier did not affect the survival and neurological outcome in the patients with ROSC after OHCA [14]. As expected, the similar result was showed in our study. Moreover, we performed the additional analysis to reveal the patients with better therapeutic response for the PCI-first strategy. We investigated the patients classified by the location of coronary artery stenosis and LVEF because PCI has been more effective for the patients with a large ischemic burden and reduced LVEF [15, 16]. However, there were no statistically significant differences in the survival and neurological outcome even in the patients with large ischemic burden such as having large LAD stenosis, multivessel diseases, and reduced LVEF. Previous studies have recommended that the interval from CA to target core temperature should be within 6 h to make TTM more effective [1, 4]. Although the PCI-first group significantly delayed the induction of TTM in this study, it took no more than 6 h. This may be a reason why there was no significant difference between the two groups in the present study.

2.4.1 Study Limitation

Several limitations of this study should be acknowledged. First, this study was observational study. Therefore, the results should be confirmed in future studies. Second, there may be some differences in methods of TTM between institutions. Third, the data of precise time about reperfusion was not corrected in this study.

2.5 Conclusion

The present multicenter registry studies indicate that the timing of PCI did not significantly affect survival and neurological outcome in OHCA patients although PCI-first strategy delayed the induction of TTM. The application of both treatment seems to be superior to their sequences for the particular OHCA patients.

Acknowledgments We thank all of the members of the J-PULSE-Hypo study group who participated in this multicenter observational study: Department of Cardiovascular Medicine, Division of Cardiovascular Care Unit, National Cerebral and Cardiovascular Center, Osaka; Department of Cardiology, Cardiopulmonary Resuscitation, and Emergency Cardiovascular Care, Surugadai Nihon University Hospital, Tokyo; Emergency and Critical Care Center, Sapporo City University Hospital, Sapporo; Critical Care and Emergency Medical Center, Yokohama City University Medical Center, Yokohama; Emergency Medicine, Osaka Mishima Emergency Critical Care Center, Osaka; Emergency and Critical Care Medicine Center, Osaka City General Hospital, Osaka; Division of Cardiology, Osaka Police Hospital, Osaka; Senri Critical Care Medical Center, Saiseikai Senri Hospital, Osaka; Department of Cardiology, Sumitomo Hospital, Osaka; Emergency and Critical Care Center, Kagawa University Hospital, Kagawa; Advanced Medical Emergency and Critical Care Center, Yamaguchi University Hospital, Yamaguchi; Division of Cardiology, Kokura Memorial Hospital, Kokura; and Department of Emergency Medicine, Saga University Hospital, Saga.

References

1. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346:549–56.
2. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346:557–63.
3. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med. 2013;369:2197–206.
4. Nagao K, Kikushima K, Watanabe K, et al. Early induction of hypothermia during cardiac arrest improves neurological outcomes in patients with out-of-hospital cardiac arrest who undergo emergency cardiopulmonary bypass and percutaneous coronary intervention. Circ J. 2010;74:77–85.
5. Knafelj R, Radsel P, Ploj T, Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. Resuscitation. 2007;74:227–34.
6. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv. 2010;3:200–7.
7. Yokoyama H, Nagao K, Hase M, et al. Impact of therapeutic hypothermia in the treatment of patients with out-of-hospital cardiac arrest from the J-PULSE-HYPO study registry. Circ J. 2011;75:1063–70.
8. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation. 1991;84:960–75.
9. Emergency Cardiovascular Care Committee. Subcommittees and task forces of the American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2005;112:IV1–IV203.
10. Vaillant C, Leurent G, Garlantezec R, et al. Coronary angioplasty is associated with a better neurological outcome in the era of modern management of out-of-hospital cardiac arrest. Int J Cardiol. 2013;169:e91–2.

11. Dumas F, Bougouin W, Geri G, et al. Emergency PCI in post-cardiac arrest patients without ST-segment elevation pattern: insights from the PROCAT II registry. JACC Cardiovasc Interv. 2016;9:1011.
12. Dumas F, White L, Stubbs BA, Cariou A, Rea TD. Long-term prognosis following resuscitation from out of hospital cardiac arrest: role of percutaneous coronary intervention and therapeutic hypothermia. J Am Coll Cardiol. 2012;60:21–7.
13. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132:S465–82.
14. Hagiwara S, SOS-KANTO 2012 Study Group. Study on the priority of coronary arteriography or therapeutic hypothermia after return of spontaneous circulation in patients with out-of-hospital cardiac arrest: results from the SOS-KANTO 2012 study. Intern Emerg Med. 2016;11:577.
15. M Emond MBM, Davis KB, Fisher LD, Holmes DR, Chaitman BR, Kaiser GC, Alderman E, Killip T. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. Circulation. 1994;90:2645.
16. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE) trial nuclear substudy. Circulation. 2008;117:1283–91.

Chapter 3
Prognostic Value of Early Lactate Clearance in Patients with Post-Cardiac Arrest Syndrome

Kei Hayashida

Abstract The current guidelines emphasize that early prognostication of outcome is an essential component of post-cardiac arrest care. Lactate has been studied as an indicator of critical illness severity. Several studies reported that initial lactate level obtained immediately after hospital arrival was an independent predictor of survival and neurological outcomes in patients with post-cardiac arrest syndrome (PCAS). Recent studies also described that serial lactate measurements in early after-hospital admission could be more useful than a single lactate measurement as a predictor of outcome in those patients. Thus, we conducted an ad hoc analysis of the prospective, multicenter observational study to test the hypothesis that early lactate reduction within 6 h after admission could be a prognostic factor for the outcomes in PCAS. Among the eligible patients (n = 1482), the overall 30-day proportions for survival and good neurological outcome were 29.7% and 16.7%, respectively. Among the study patients, there were significant differences in age, ROSC prior to hospital arrival, epinephrine usage during ACLS, mechanical circulatory support, therapeutic hypothermia, and lactate levels at 0 and 6 h among the lactate clearance quartiles. Of note, patients in the quartile 4 group had the highest initial lactate level. Multivariate logistic regression analyses showed that lactate clearance quartile was an independent predictor of the 30-day survival and good neurologic outcome. In the Cox proportional hazards model, the frequency of mortality during 30 days was markedly higher for patients with lactate clearance in the 1st (hazard ratio, 3.12; 95% CI, 2.14–4.53), 2nd (2.13; 1.46–3.11), and 3rd quartile (1.49; 1.01–2.19) than those in the 4th quartile. In summary, effective lactate reduction over the first 6 h of post-cardiac arrest care was associated with survival and good neurologic outcome independent of the initial lactate level.

Keywords Post-cardiac arrest syndrome · Prognostication · Lactate · Lactate clearance

K. Hayashida
Department of Emergency and Critical Care Medicine, School of Medicine, Keio University, Tokyo, Japan

M. Aibiki, S. Yamashita (eds.), *A Perspective on Post-Cardiac Arrest Syndrome*,
https://doi.org/10.1007/978-981-13-1099-7_3

3.1 Introduction

Sudden cardiac arrest is one of the leading causes of death worldwide [1]. Despite advances in the management of cardiac arrest patients, improvement in the rates of survival to hospital discharge has been extremely limited, and more than half of the survivors exhibit lasting neurologic deficits [2, 3]. The current guidelines emphasize that early prognostication of outcome is an essential component of post-cardiac arrest care [4]. Early and accurate prediction of cardiac arrest outcome can help clinicians and families to make a better-informed decision for the patient's healthcare. Thus, the main objective of predictive test of survivors with PCAS immediately after return of spontaneous resuscitation (ROSC) is to establish the survival to discharge with intact neurological function [5].

3.2 Pathophysiology and Current Treatment for Post–Cardiac Arrest Syndrome

The PCAS is characterized as systemic illness from ischemic-reperfusion injury combined with the pathophysiologic derangements. The greatest proportion of post-cardiac arrest mortality and morbidity is caused by global ischemic brain injury [6]. The pathophysiological mechanisms responsible for brain injury after ROSC include excitotoxicity, free radical formation, pathological activation of proteases, and cell death signaling [2, 7]. Managements for PCAS patients include optimizing oxygenation and organ perfusion, targeted temperature management (TTM), and treating the underlying etiology of arrest. Current guidelines regarding PCAS management recommend measuring serial lactate levels in postarrest patients to ensure adequate perfusion, based on evidence from other diseases such as sepsis [4].

3.3 Prognostication After Cardiac Arrest

Early and accurate prognostication after cardiac arrest can help with the optimal management after hospital admission for patients with PCAS and minimize related emotional and financial costs for their families. Over the last few decades, several studies have shown the utility of several prognostic tools of PCAS outcome, such as clinical examination, biochemical markers, electrophysiological testing, and neuroimaging. Clinical findings such as the absence of motor response, presence of myoclonus status epilepticus, and lack of brainstem reflexes have been widely used for the prognostication after successful CPR. Blood biomarkers (e.g., neuron-specific enolase [NSE] and soluble 100-β protein) are useful for coma prognostication, but results vary among commercial laboratory assays, and

applying one single cutoff level for poor prognostication is not recommended. Electroencephalogram monitoring after resuscitation can contribute to the prediction of both good and poor neurological outcome. Neuroimaging tests such as computer tomography (CT) (e.g., the loss of distinction between gray and white matter), position emission tomography (PET) (e.g., reduced glucose metabolism), and diffusion MRI are emerging as promising tools for prognostication. However their precise roles need further study. This multimodal approach might offer the best outcome predictive performance for prognostication of comatose survivors from PCAS [8].

3.4 Role of Lactate Metabolism in Cellular Stress and Recovery

In the critical care setting, lactate is frequently measured in several diseases, usually with the goal of detecting tissue hypoxia. Lactate is a crucial metabolite in the glycolysis and oxidative phosphorylation. Under stable conditions, glycolysis and oxidative phosphorylation steadily metabolize glucose. Because the rate of glycolysis can increase two to three times faster than oxidative phosphorylation, glycolysis can quickly provide far more adenosine triphosphate (ATP). Excess pyruvate will rapidly accumulate and is converted to lactate in order for glycolysis to proceed. Under recovery conditions, lactate is diverted into pyruvate. These reactions (both directions) are catalyzed by the lactate dehydrogenase (LDH). Thus, LDH catalyzes the conversion of lactate to pyruvic acid and back, as it converts NAD^+ to NADH and back (Fig. 3.1). When rapidly large amounts of energy are required, such as under circumstances of cellular stress, lactate serves as a critical buffer that allows glycolysis to accelerate.

Increased lactate levels may represent tissue hypoxia, accelerated aerobic glycolysis driven by excess adrenergic stimulation, or decreased clearance due to hepatic dysfunction. Several experimental studies have confirmed the relationship between the production of lactate and tissue hypoxia by reducing the components of systemic oxygen delivery (cardiac output, oxygen saturation, and hemoglobin level) until the extraction of oxygen can no longer maintain oxygen availability to the cells to meet their demands [9, 10]. When oxygen delivery reduced at a critical level, oxygen consumption becomes limited by oxygen delivery with the concomitant increase of blood lactate levels. In an experimental study of cardiac tamponade by Zhang and colleagues [10], it was demonstrated that resolution of the supply-dependent state of oxygen consumption by resolving the tamponade was associated with an increment of oxygen consumption to baseline levels and normalization of lactate levels. Moreover, impaired aerobic metabolism and aggravation of oxidative stress caused by mitochondrial dysfunction have been implicated as causes of neurological deficits following cardiac arrest [11–13]. Pyruvate dehydrogenase (PDH) is the critical rate-limiting mitochondrial matrix enzyme linking glycolysis to the

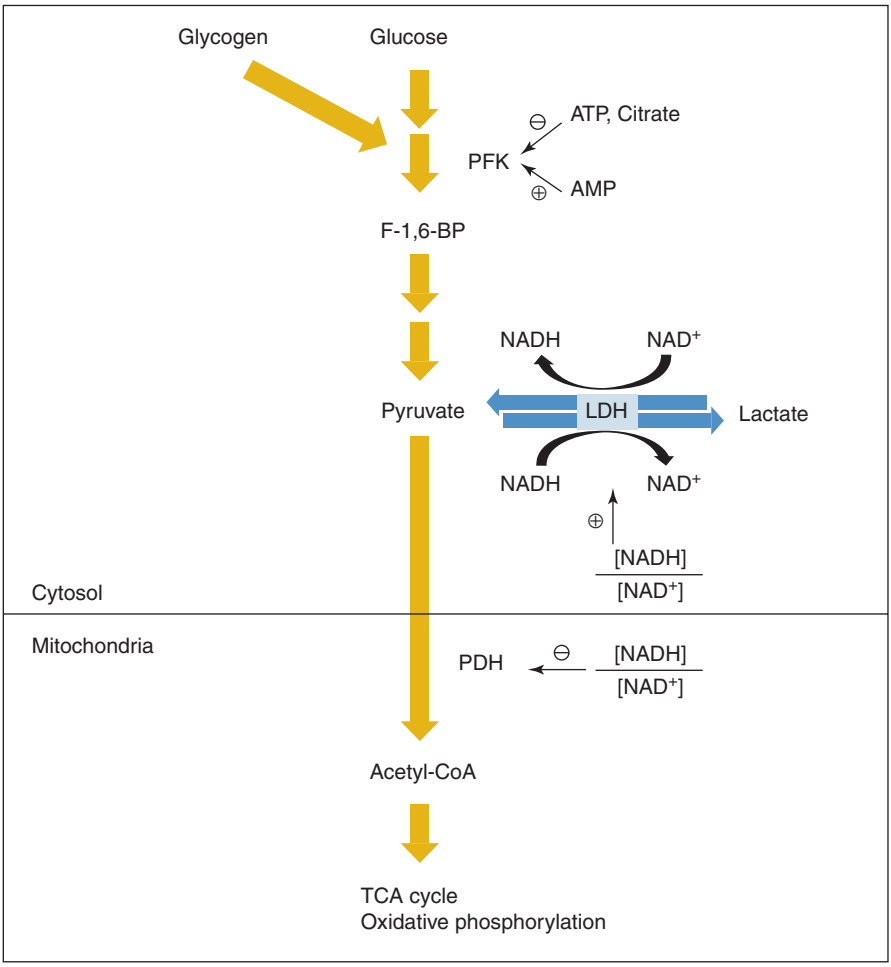


Fig. 3.1 Metabolic pathways of Pyruvate/Lactate. *PFK* phosphofructokinase; *F-1,6-BP* fructose 1,6-bisphosphate; *NADH* nicotinamide adenine dinucleotide; *LDH* lactate dehydrogenase; *PDH* pyruvate dehydrogenase

tricarboxylic acid (TCA) cycle. PDH is inhibited stimulated by NADH and acetyl-CoA. (Fig. 3.1). In tissue hypoxia, lactate is overproduced and underutilized as a result of impaired mitochondrial oxidation. Even if systemic oxygen delivery recovers to normal range, microcirculatory dysfunction can cause tissue hypoxia and hyperlactatemia. Hyperoxia-induced oxidative inactivation of PDH has been suggested as a culprit in the loss of cerebral aerobic metabolism and neurological deficit after cardiac arrest [11, 14]. Although there are still ongoing discussions, a recent science has focused on the presence of mitochondrial dysfunction in critically ill that could limit pyruvate metabolism (and thus increase lactate levels) in the absence of limited oxygen availability [15, 16].

3.5 Role of Lactate in the Critical Care Setting

Blood lactate concentration is generally recognized as a hemodynamic indicator and target for resuscitation in the critically ill for decades. In several critical illnesses, increased blood lactate levels have been related to morbidity and mortality. The measurement of lactate levels both in the emergency department and in the ICU is shown to be helpful for risk stratification [17]. In addition, Jansen and colleagues demonstrated that the duration and area under the curve of increased lactate levels are related to both morbidity and mortality in heterogeneous intensive care unit patients [18]. Several clinical conditions have been associated with impaired clearance of lactate. Nguyen and colleagues showed a significant association between lactate clearance and biomarkers of pro- and anti-inflammation, coagulation, apoptosis, and further with multiorgan dysfunction and mortality in severe sepsis and septic shock [19]. Also, lactate clearance has been shown to be impaired in patients with liver dysfunction [20] and after cardiac surgery [21]. A body of evidence suggests that global tissue hypoxia plays a crucial role in the complex mechanisms leading to the endothelial response in severe sepsis and septic shock rather than a terminal event. Further, given the well-established relationship with the inadequate tissue oxygenation and with morbidity and mortality, lactate levels could represent a useful goal of initial resuscitation in many clinical conditions.

3.6 Lactate Levels After Successful Resuscitation from Cardiac Arrest

Circulatory arrest and the hypocirculatory state during cardiopulmonary resuscitation (CPR) can contribute to lactic acidosis. Oxygen deficiency leads to anaerobic metabolism and therefore to lactate overproduction. Concurrently, the impaired liver function due to profound ischemia state results in reduced lactate clearance [22]. Carden and colleagues reported in detail the time course of linear increase in blood lactate level during CPR in an animal cardiac arrest model, suggesting that delayed ROSC and/or poor quality of CPR may lead to an increased blood lactate concentration [23]. Decrease in lactate is a surrogate marker for adequate tissue perfusion after ROSC and potentially serves as an endpoint for resuscitation. Two retrospective studies have demonstrated that effective clearance was associated with decreased mortality [24, 25]. Starodub and colleagues measured lactate levels at time of hospital admission and 12 and 24 h after ROSC in PCAS patients treated with therapeutic hypothermia [26]. They observed no difference in initial lactate levels between survivors and nonsurvivors; however, lactate levels at 12 and 24 h after ROSC were significantly lower in survivors. Donnino and colleagues reported that lower lactate levels at 0, 12, and 24 h as well as a greater lactate reduction at 12 h were associated with improved survival and good neurologic outcomes in patients with PCAS in a four-center prospective observational study [27].

Furthermore, Ikeda and colleagues have demonstrated that pyruvate dehydrogenase (PDH) activity was markedly depressed in post-cardiac arrest patients [28]. Taken together, it is reasonable to hypothesize that effective lactate reduction early after hospital admission can be a prognostic factor for outcomes and a target for resuscitation in PCAS patients.

3.7 Can Early Lactate Clearance Predict the Outcomes in Patients with PCAS?

Based on the abovementioned backgrounds, we sought to verify the hypothesis that early lactate reduction is a prognostic factor for outcomes and a target for resuscitation in PCAS patients. To determine whether early lactate reduction during PCAS care can be associated with improved survival and good neurologic outcome at 30 days after ROSC in patients who suffered OHCA, we conducted an ad hoc data analysis of a prospective, multicenter observational study [29].

3.7.1 Study Design and Settings

We performed the survey of survivors after OHCA in the Kanto area, including the Tokyo Prefecture of Japan in 2012 (SOS-KANTO 2012 study). Briefly, SOS-KANTO study was a prospective, multicenter observational study consisting of 16,452 patients who suffered OHCA and were transported to the 67 emergency hospitals by emergency medical service (EMS) personnel between January 2012 and March 2013.

The inclusion criteria of the present study were (1) hospital admission after achieving ROSC and (2) lack of severe disability as activities of daily living before cardiac arrest. The exclusion criteria were (1) admission to hospitals where the frequency of serial lactate measurements after ICU admission was less than 20%, (2) age was less than 18 years, and (3) cardiac arrest was caused by the following diseases: acute aortic dissection/rupture, subarachnoid hemorrhage, and obvious exogenous factor including trauma, burn, asphyxia, drowning, accidental hypothermia, and drug overdose, because these can affect liver metabolism and/or hypoxic mechanism and production and clearance of lactate.

The primary endpoint was 30-day survival, and the secondary endpoint was good neurologic outcome 30 days after cardiac arrest. The cerebral performance category (CPC) scale was used to categorize neurologic outcomes: CPC 1, good performance; CPC 2, moderate disability; CPC 3, severe disability; CPC 4, comatose or persistent vegetative status; and CPC 5, brain death or death. CPC 1 and 2 were defined as good neurologic recovery. CPC scores were further dichotomized into good (CPC 1 or 2) and poor (CPC 3, 4, or 5) outcomes. To collect 1-month follow-up data, the institutional researchers collected inhospital information including sur-

vival and neurologic outcome. If the patients were discharged from the hospitals or transferred out to rehabilitation hospitals, the institutional researchers collected the information by phone.

3.7.2 Definition of Early Lactate Clearance

Early lactate clearance was defined as the percent change in lactate level 6 h after a baseline measurement. It was calculated using the following formula: lactate at hospital admission (hour 0) minus lactate at hour 6, divided by lactate at hospital admission (hour 0), which is then multiplied by 100. A positive value denotes a decrease or clearance of lactate, whereas a negative value denotes an increase in lactate after 6 h of intervention.

3.7.3 Data Collection

Pre- and inhospital data were prospectively collected. Prehospital information was collected by EMS providers and included age, sex, preadmission functional status, witness status, presence of bystander CPR, location of cardiac arrest, cause of cardiac arrest (coded as cardiogenic or noncardiogenic), initial cardiac rhythm, airway management by EMS personnel, prehospital automated external defibrillator (AED) attempt, time interval from EMS call to arrival at the hospital, and achievement of ROSC prior to hospital arrival. The inhospital information was collected by institutional researchers: ROSC subsequent to arrival at the hospital, hospital admission, laboratory data obtained immediately after hospital arrival, medications and post-resuscitation treatment, duration of hospital stay, and neurologic outcome at 30 days after CA. Post-resuscitation interventions included therapeutic hypothermia, renal replacement therapy, and mechanical circulatory support. In this SOS-KANTO 2012 study, physicians were encouraged to measure lactate levels at 0 and 6 h if they deemed it appropriate in each individual case.

3.7.4 Statistical Analyses

Distributions of continuous variables were compared and evaluated with the use of the t-test (or analysis of variance). The chi-square test or Fisher exact test was used for comparisons of binary variables. The linear trend across the levels of a variable was tested by the Cochran-Armitage trend test. The study population was sorted by increasing lactate clearance values and divided into four groups by lactate clearance quartiles (Table 3.1). For primary analyses, multivariate logistic regressions were used for adjusting selected covariates to assess the associations between lactate

Table 3.1 Characteristics and pre−/inhospital information by lactate clearance quartile [29]

Variables	1st quartile: LC ≤ 22.2% (n = 136)	2nd quartile: 22.2–56.8 (n = 136)	3rd quartile: 56.8–76.3 (n = 136)	4th quartile: LC > 76.3% (n = 135)	P value
Lactate clearance, %	−23.0 ± 69.0	41.6 ± 10.2	67.1 ± 5.4	84.2 ± 5.0	–
Prehospital characteristics					
Age, years	69 ± 15	64 ± 14	62 ± 16	63 ± 18	0.002
Male sex	100 (73.5)	104 (76.5)	97 (71.3)	93 (68.9)	0.55
Preadmission functional status					0.40
No disability	101 (74.3)	104 (76.5)	100 (73.5)	105 (77.8)	
Mild disability	17 (12.5)	9 (6.6)	9 (6.6)	11 (8.1)	
Unknown	18 (13.2)	23 (16.9)	27 (19.9)	19 (14.1)	
Witness	101 (74.3)	101 (74.3)	107 (78.7)	99 (73.3)	0.74
CPR initiated by bystander	57 (41.9)	66 (48.5)	60 (44.1)	53 (39.3)	0.47
Cardiac etiology	103 (75.7)	111 (81.6)	105 (77.2)	99 (73.3)	0.43
Location of cardiac arrest					0.18
Home	81 (59.6)	65 (47.8)	61 (44.9)	75 (55.6)	
Nursing home	6 (4.4)	6 (4.4)	1 (0.7)	2 (1.5)	
Public building	35 (25.7)	49 (36.0)	56 (41.2)	41 (30.7)	
Others	14 (10.3)	16 (11.8)	18 (13.2)	17 (12.6)	
Initial shockable rhythm	53 (39.0)	49 (36.0)	53 (39.0)	47 (34.8)	0.86
Prehospital procedure by EMS					
Airway management	130 (95.6)	127 (93.4)	127 (93.4)	126 (93.3)	0.83
Defibrillation by AED	67 (49.3)	66 (48.5)	66 (50.0)	60 (44.4)	0.80
Time from call to hospital arrival, min	35 ± 12	35 ± 13	35 ± 11	33 ± 10	0.21
ROSC prior to hospital arrival	35 (25.7)	59 (43.4)	52 (38.2)	60 (44.4)	0.005
Drugs and interventions after hospital arrival					
Epinephrine use during ACLS	102 (75.0)	81 (59.6)	89 (65.4)	74 (54.8)	0.004
Steroids usage	1 (0.7)	2 (1.5)	1 (0.7)	1 (0.7)	0.90
Anticonvulsants	16 (11.8)	22 (16.2)	15 (11.0)	26 (19.3)	0.18
Antipyretics	6 (4.4)	9 (6.6)	3 (2.2)	11 (8.1)	0.14
Mechanical circulatory support	47 (34.6)	54 (39.7)	46 (33.8)	24 (17.8)	0.001
Therapeutic hypothermia	57 (41.9)	84 (61.8)	90 (66.2)	85 (63.0)	<0.001
Renal replacement therapy	15 (11.0)	10 (7.4)	7 (5.1)	13 (9.6)	0.31

Table 3.1 (continued)

Variables	1st quartile: LC ≤ 22.2% (n = 136)	2nd quartile: 22.2–56.8 (n = 136)	3rd quartile: 56.8–76.3 (n = 136)	4th quartile: LC > 76.3% (n = 135)	P value
Lactate concentrations					
Lactate at hour 0, mmol/L	8.5 ± 5.6	9.6 ± 5.2	10.3 ± 4.6	11.0 ± 4.9	<0.001
Lactate at hour 6, mmol/L	9.4 ± 6.0	5.7 ± 3.3	3.4 ± 1.6	1.7 ± 0.9	<0.001

LC lactate clearance. Continuous variables were presented as mean ± SD. Categorical variables were presented as frequencies (%)

clearance quartiles and primary and secondary outcomes. Independent variables were selected as follows: lactate clearance quartiles, lactate concentration at hospital admission, age, sex, witness status, CPR initiated by bystander, initial shockable rhythm, cardiac etiology, airway management by EMS, AED attempted by EMS, time interval from EMS call to hospital arrival, ROSC achieved prior to hospital arrival, epinephrine usage during advanced cardiovascular life support (ACLS), and treatments after hospital admission including therapeutic hypothermia, mechanical circulatory support, renal replacement therapy, steroids usage, anticonvulsants usage, and antipyretics usage. Receiver operating characteristic (ROC) curve analyses were performed for evaluating the accuracy of lactate clearance in differentiating between survivors and nonsurvivors at 30 days. The area under curves (AUCs) in the ROC and their 95% CIs was calculated.

As a secondary analysis, the Kaplan-Meier method and logrank tests were used to compare the four lactate clearance quartiles. The Cox proportional hazards regression model was used to investigate whether lactate clearance was associated with all-cause death. All abovementioned covariates were included in the model.

All statistical tests used a significance level of 0.05 and were two-sided. All data were analyzed with SPSS version 23.0 (SPSS, Chicago, IL).

3.8 Results

3.8.1 Characteristics of Study Patients

The study flowchart is presented in Fig. 3.2. A total of 16,452 OHCA patients were identified during the study period. Of those, 1482 PCAS patients were eligible according to the inclusion criteria. The overall 30-day survival proportion and good neurologic outcome were 29.7% and 16.7%, respectively. After excluding 409 patients had data missing for mandatory elements which were included in the multivariate regression model; 543 PCAS patients were included in the final analyses

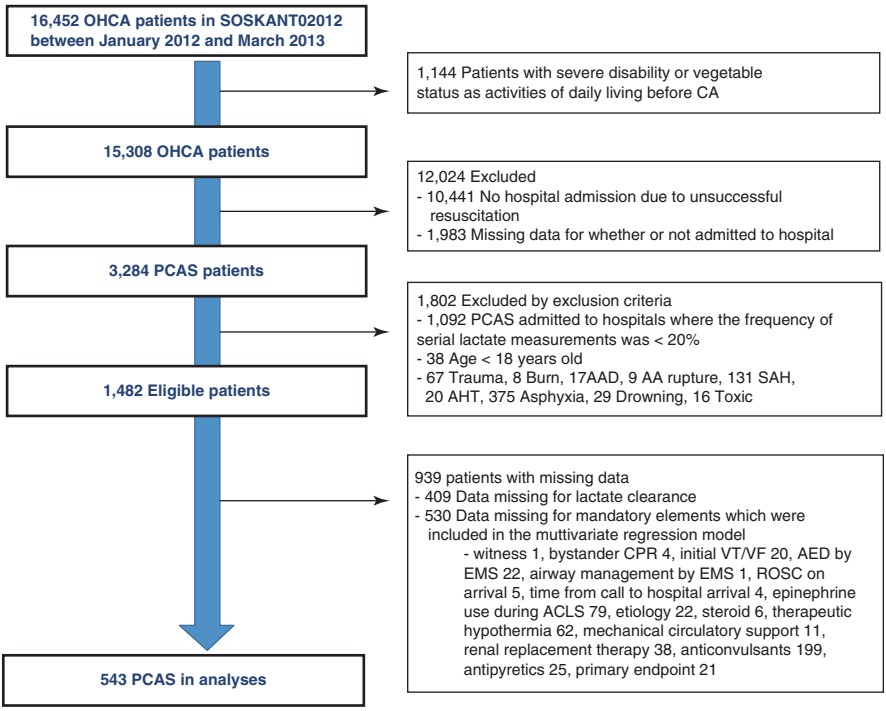


Fig. 3.2 Patient selection. *AA rupture* acute aortic rupture; *AAD* acute aortic dissection; *ACLS* advanced cardiovascular life support; *AED* automated external defibrillator; *AHT* accidental hypothermia; *CA* cardiac arrest; *EMS* emergency medical service; *SAH* subarachnoid hemorrhage; *VT/VT* ventricular fibrillation and pulseless ventricular tachycardia

(Fig. 3.2). Table 3.1 shows the characteristics by lactate clearance quartile. The lactate clearance quartiles were − 23.0% ± 69.0%, 41.6% ± 10.2%, 67.1% ± 5.4%, and 84.2% ± 5.0%, respectively. There were significant differences in age, ROSC prior to hospital arrival, epinephrine usage during ACLS, mechanical circulatory support, therapeutic hypothermia, and lactate levels at 0 and 6 h among the lactate clearance quartiles (Table 3.1). The distribution of lactate clearance is shown in Fig. 3.3. Among the final analyzed patients, the 30-day survival was observed in 256 of 543 patients (47.1%) and good neurologic outcome in 149 of 543 patients (27.4%).

3.8.2 Early Lactate Clearance Is Associated with Improved Outcomes in Patients with PCAS

The increasing lactate clearance is significantly associated with the increasing survival proportion (quartile 1, 29.4%; quartile 2, 42.6%; quartile 3, 51.5%; quartile 4, 65.2%; Cochran-Armitage trend test, $p < 0.001$) (Fig. 3.4). Multivariate analysis showed that lactate clearance in quartiles 3 and 4 was an independent predictor of survival (Table 3.2). Similarly, a significant trend was found for a good neurologic

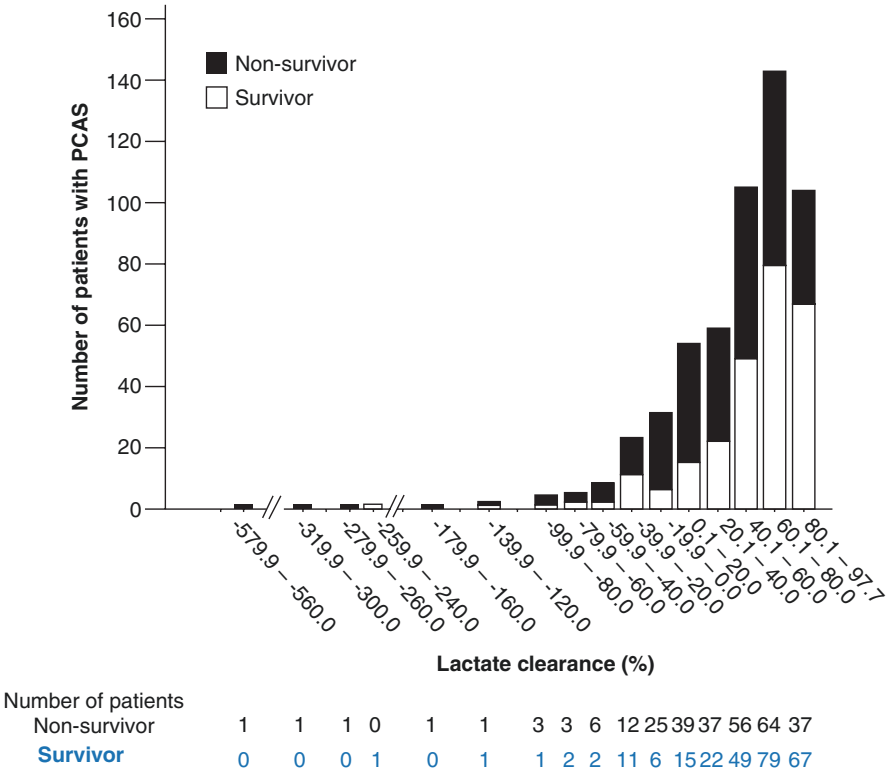


Fig. 3.3 Distribution of early lactate clearance among survivors and non-survivors

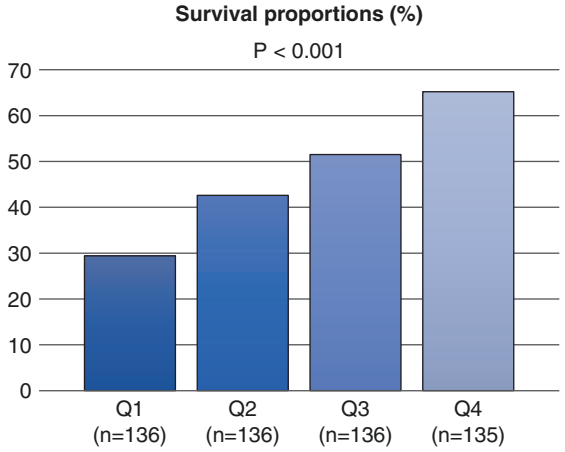


Fig. 3.4 Association between the quartiles of lactate clearance and the 30-day survival proportion after cardiac arrest and successful cardiopulmonary resuscitation

outcome with increasing lactate clearances (quartile 1, 14.0%; quartile 2, 30.1%; quartile 3, 32.4%; quartile 4, 33.3%; Cochran-Armitage trend test, $p < 0.001$) (Fig. 3.5). Multivariate analysis revealed that lactate clearances were significant predictors of good neurologic outcome (Table 3.3).

Table 3.2 Unadjusted and adjusted OR of early lactate clearance for survival at 30 days after hospital admission [29]

Univariate analysis	*OR*	*95% CI*	*P value*
Quartile 1 (reference)	1.0	ref.	–
Quartile 2	1.79	1.08–2.95	0.02
Quartile 3	2.55	1.55–4.19	<0.001
Quartile 4	4.49	2.70–7.49	<0.001
Multivariate analysis	*Adjusted OR*	*95% CI*	*P value*
Quartile 1 (reference)	1.0	ref.	–
Quartile 2	1.56	0.82–2.92	0.17
Quartile 3	3.17	1.67–5.60	<0.001
Quartile 4	6.67	3.37–13.20	<0.001

OR odds ratio; *CI* confidence intervals

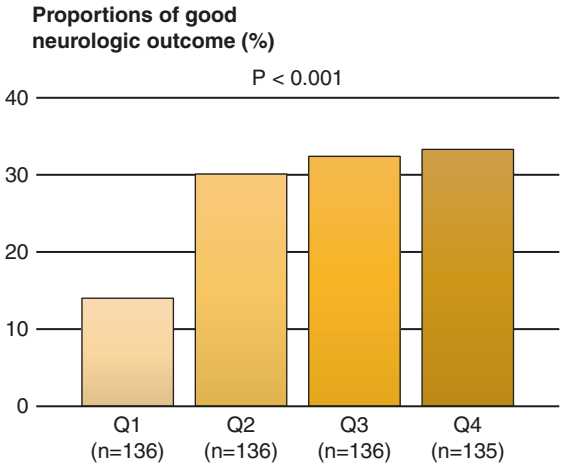


Fig. 3.5 Association between the quartiles of lactate clearance and the proportion of 30-day good neurologic outcome after cardiac arrest and successful cardiopulmonary resuscitation

Table 3.3 Unadjusted and adjusted OR of early lactate clearance for good neurological outcome at 30 days after hospital admission [29]

Univariate analysis	*OR*	*95% CI*	*P value*
Quartile 1 (reference)	1.0	ref.	–
Quartile 2	2.66	1.45–4.88	0.002
Quartile 3	2.95	1.61–5.38	<0.001
Quartile 4	3.08	1.69–5.63	<0.001
Multivariate analysis	*Adjusted OR*	*95% CI*	*P value*
Quartile 1 (reference)	1.0	ref.	–
Quartile 2	3.10	1.44–6.67	0.004
Quartile 3	3.92	1.79–8.55	0.001
Quartile 4	4.54	2.00–10.34	<0.001

OR odds ratio; *CI* confidence intervals

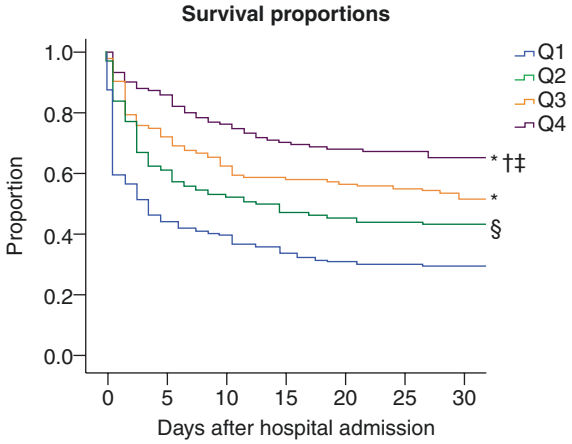


Fig. 3.6 The Kaplan-Meier analysis based on lactate clearance quartile (Q; log-rank test; $p < 0.001$). *$p < 0.001$ vs. Q1, †$p < 0.05$ vs. Q2, ‡$p < 0.001$ vs. Q3, §$p < 0.01$ vs. Q1

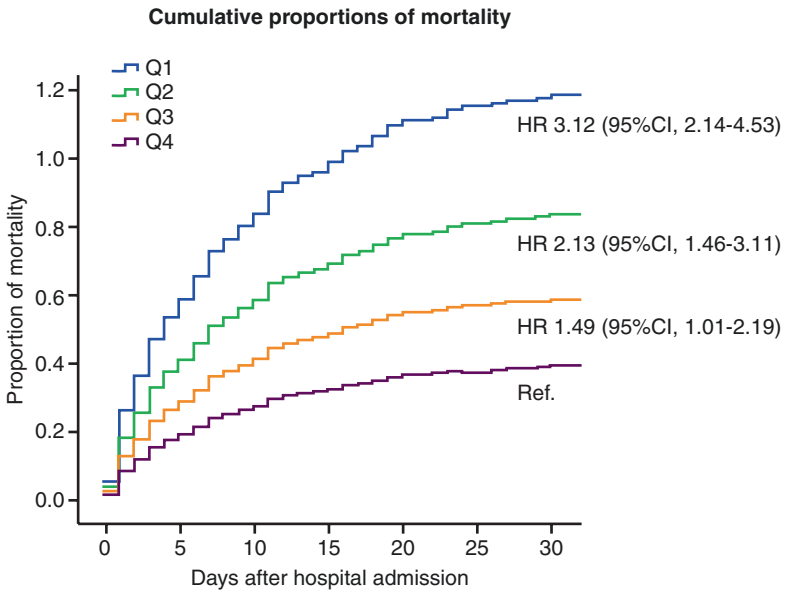


Fig. 3.7 The Cox proportional hazards model of mortality during follow-up according to the quartiles of early lactate clearance. *HR* hazard ratio

The Kaplan-Meier survival analysis showed a survival benefit during 30 days for patients in the higher lactate clearance quartiles (logrank test, $p < 0.001$) (Fig. 3.6). In the Cox proportional hazards regression model, the cumulative proportional hazards were significantly higher for patients with lactate clearance in the 1st (hazard ratio [HR], 3.12; 95% CI, 2.14–4.53; $p < 0.001$), 2nd (HR, 2.13; 95% CI, 1.46–3.11; $p < 0.001$), and 3rd (HR, 1.49; 95% CI, 1.01–2.19; $p = 0.04$) than those with lactate clearance in the 4th quartile (Fig. 3.7).

In a receiver operating characteristic (ROC) analysis, the area under the curve (AUC) revealed that lactate clearance cutoff of 51.8% provided optimal sensitivity and specificity for predicting 30-day survival (AUC, 0.65; 95% CI, 0.60–0.70; sensitivity, 67.2%; specificity, 57.1%).

In summary, our study suggested that effective lactate clearance within the first 6 h during post-cardiac arrest management was significantly associated with survival and good neurologic outcomes in patients with PCAS independently of initial lactate concentration [29]. Our results also provide evidence that the design and interpretation of future clinical studies should consider the early stages of post-cardiac arrest care. Further research is required to clarify the mechanisms underlying the role of lactate and its clearance, such as the complex interaction between increased removal, decreased production, and lactate dilution.

3.8.3 Limitation of this Study

There were several limitations in this study. First, 63.4% (939/1482) of the eligible patients had missing data, resulting in a reduced statistical power. Given that patients with data missing had an older age, a lower proportion of initial shockable rhythm, cardiac etiology, and received substantial treatments after ICU admission, it is possible that mortality within 6 h after admission led to a lack of lactate measurement at 6 h in these patients and that the role of lactate clearance could be limited to some patients with a good prognosis. It is conceivable that the use of lactate clearance might be applicable to a population of successfully resuscitated adult patients with nontraumatic OHCA. Second, healthcare providers were not blinded to clinical lactate measurements; therefore, care might have been altered based on the available data. Third, we could not obtain clinical data related to the causes of hyperlactatemia. Lactate clearance might be affected by underlying comorbidities such as sepsis, liver disease, and acute/chronic kidney injury in patients. Finally, as with any observational study, the association between effective lactate reduction and good outcomes does not necessarily prove causality and might be confounded by unmeasured factors.

3.9 Conclusions

Greater percentage of lactate reduction within 6 h after admission is associated with improved survival and good neurological outcome in patients with PCAS. Although the early lactate clearance during post-CA care as a target of resuscitation warrants further research, the serial measurement of blood early after admission can be a promising tool for prognostication and should be included in the routine management in patients with PCAS.

References

1. Field JM, Hazinski MF, Sayre MR, Chameides L, Schexnayder SM, Hemphill R, Samson RA, Kattwinkel J, Berg RA, Bhanji F, Cave DM, Jauch EC, Kudenchuk PJ, Neumar RW, Peberdy MA, Perlman JM, Sinz E, Travers AH, Berg MD, Billi JE, Eigel B, Hickey RW, Kleinman ME, Link MS, Morrison LJ, O'Connor RE, Shuster M, Callaway CW, Cucchiara B, Ferguson JD, Rea TD, Vanden Hoek TL. Part 1: executive summary: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122:S640–56.
2. Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Bottiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT Jr, Merchant RM, Morley P, Morrison LJ, Nadkarni V, Peberdy MA, Rivers EP, Rodriguez-Nunez A, Sellke FW, Spaulding C, Sunde K, Vanden Hoek T. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation. 2008;118:2452–83.
3. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A, Stiell I. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300:1423–31.
4. Callaway CW, Donnino MW, Fink EL, et al. Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132:S465–82.
5. Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, Nadkarni VM, Abella BS, Adrie C, Berg RA, Merchant RM, O'Connor RE, Meltzer DO, Holm MB, Longstreth WT, Halperin HR. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. Circulation. 2011;124:2158–77.
6. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004 Nov;30(11):2126–8.
7. Neumar RW. Molecular mechanisms of ischemic neuronal injury. Ann Emerg Med. 2000;36(5):483–506.
8. Asgari S, Moshirvaziri H, Scalzo F, Ramezan-Arab N. Quantitative measures of EEG for prediction of outcome in cardiac arrest subjects treated with hypothermia: a literature review. J Clin Monit Comput. 2018. https://doi.org/10.1007/s10877-018-0118-3. [Epub ahead of print].
9. Cain SM. Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. Am J Phys. 1965;3:604–8.
10. Zhang H, Vincent JL. Oxygen extraction is altered by endotoxin during tamponade-induced stagnant hypoxia in the dog. Circ Shock. 1993;3(3):168–76.
11. Boaert Y, Sheu K, Hof P, et al. Neuronal subclass-selective loss of pyruvate dehydrogenase immunoreactivity following canine cardiac arrest and resuscitation. Exp Neurol. 2000;161:115–26.
12. Vaagenes P, Ginsberg M, Ebmeyer U. Cerebral resuscitation from cardiac arrest: pathophysiologic mechanisms. Crit Care Med. 1996;24:S57–68.
13. Pulsinelli W, Levy D, Duffy T. Regional cerebral blood flow and glucose metabolism following transient forebrain ischemia. Ann Neurol. 1982;11:499–502.
14. Zaidan E, Sims N. Selective reductions in the activity of the PDH complex in mitochondria isolated from brain subregions following forebrain ischemia in rats. J Cereb Blood Flow Metab. 1993;13:98–104.

15. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002;360(9328):219–23.
16. Crouser ED, Julian MW, Blaho DV, Pfeiffer DR. Endotoxin-induced mitochondrial damage correlates with impaired respiratory activity. Crit Care Med. 2002;30(2):276–84.
17. Jansen TC, van Bommel J, Bakker J. Blood lactate monitoring in critically ill patients: a systematic health technology assessment. Crit Care Med. 2009;37(10):2827–39.
18. Jansen TC, van Bommel J, Woodward R, Mulder PG, Bakker J. Association between blood lactate levels, sequential organ failure assessment subscores, and 28-day mortality during early and late intensive care unit stay: a retrospective observational study. Crit Care Med. 2009;37(8):2369–74.
19. Nguyen HB1, Loomba M, Yang JJ, Jacobsen G, Shah K, Otero RM, Suarez A, Parekh H, Jaehne A, Rivers EP. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. J Inflamm. 2010;7:6. https://doi.org/10.1186/1476-9255-7-6.
20. Almenoff PL, Leavy J, Weil MH, Goldberg NB, Vega D, Rackow EC. Prolongation of the half-life of lactate after maximal exercise in patients with hepatic dysfunction. Crit Care Med. 1989;3(9):870–3.
21. Mustafa I, Roth H, Hanafiah A, Hakim T, Anwar M, Siregar E, Leverve XM. Effect of cardiopulmonary bypass on lactate metabolism. Intensive Care Med. 2003;3(8):1279–85.
22. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet. 1974;2:81–4.
23. Carden DL, Martin GB, Nowak RM, Foreback CC, Tomlanovich MC. Lactic acidosis during closed-chest CPR in dogs. Ann Emerg Med. 1987;16:1317–20.
24. Kliegel A, Losert H, Sterz F, et al. Serial lactate determinations for prediction of outcome after cardiac arrest. Medicine. 2004;83(5):274–9.
25. Donnino MW, Miller J, Goyal N, et al. Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients. Resuscitation. 2007;75(2):229–34.
26. Starodub R, Abella BS, Grossestreuer AV, et al. Association of serum lactate and survival outcomes in patients undergoing therapeutic hypothermia after cardiac arrest. Resuscitation. 2013;84:1078–82.
27. Donnino MW, Andersen LW, Giberson T, et al. National Post-Arrest Research Consortium: initial lactate and lactate change in postcardiac arrest: a multicenter validation study. Crit Care Med. 2014;42:1804–11.
28. Ikeda K, Liu X, Kida K, Marutani E, Hirai S, Sakaguchi M, Andersen LW, Bagchi A, Cocchi MN, Berg KM, Ichinose F, Donnino MW. Thiamine as a neuroprotective agent after cardiac arrest. Resuscitation. 2016;105:138–44. https://doi.org/10.1016/j.resuscitation.2016.04.024. Epub 2016 May 13.
29. Hayashida K, Suzuki M, Yonemoto N, Hori S, Tamura T, Sakurai A, Tahara Y, Nagao K, Yaguchi A, Morimura N, SOS-KANTO 2012 Study Group. Early lactate clearance is associated with improved outcomes in patients with Postcardiac arrest syndrome: a prospective, multicenter observational study (SOS-KANTO 2012 study). Crit Care Med. 2017;45(6):e559–66.

Chapter 4
Indications for Targeted Temperature Management in Patients After Choking or Suicide Hanging

Yutaka Sakuda, Masaki Nagama, Shoki Yamauchi, Tadashi Iraha, Kiyohiko Kinjoh, and Kei Sakugawa

Abstract *Objective*: Patients after cardiac arrest from suffocation (airway obstruction caused by foreign body aspiration) or hanging could not have improved prognoses even after undergoing targeted temperature management (TTM). Therefore, to obtain characteristics of such patients, we retrospectively evaluated patients' data including other pathologies.

Methods: Sixty patients, who suffered cardiopulmonary arrest inside or outside our hospital from June 2009 to July 2016 and received TTM, were assessed. The patients were classified into the two groups: CPC1–CPC2 and CPC3–CPC5 at hospital discharge for parameter comparisons. JMP7.0 was used for statistical analysis, while the Wilcoxon rank sum test and χ^2 test were used for testing statistical significance.

Results: Among 60 patients receiving TTM, 40 were male and 20 female. The average age was 64. Nine patients had airway obstructions due to foreign body aspiration or hanging, while 51 patients died due to other diseases such as ventricular fibrillation, cardiac infarction, and bronchial asthma. The overall average pH upon arrival was 6.99, while the overall average serum potassium was 4.68 mEq/L. In two cases, the airway obstruction and hanging were witnessed, while four patients received bystander CPR. None of the nine patients with airway obstruction due to foreign body aspiration or hanging was evaluated as CPC1–CPC2, while 16 (31%) out of 51 patients with other diseases were neurologically favorable. All nine patients with airway obstructions were determined as poor outcomes (CPC3–CPC5), while those in the other causes were 35 out of 51 subjects (100 vs. 68%, $p = 0.0497$).

Discussion: From the results of our hospital, we assume that TTM resulted in no improvements in the outcomes of patients who suffered airway obstruction due to foreign body aspiration or hanging. In general, some facilities do not actively indicate TTM for patients who suffered airway obstructions. However, improved

Y. Sakuda (✉) · M. Nagama · S. Yamauchi · T. Iraha · K. Kinjoh · K. Sakugawa
Department of Emergency and Intensive Care Unit, Okinawa Kyodo Hospital, Okinawa, Japan

M. Aibiki, S. Yamashita (eds.), *A Perspective on Post-Cardiac Arrest Syndrome*,
https://doi.org/10.1007/978-981-13-1099-7_4

prognoses have been reported in some case reports ("The 53-year-old man who was out-of-hospital asystole recovered without a problem neurologically." Intern Emerg Med 2009;4:445–7. "A case in which TTM was used successfully in a patient with coma after cardiorespiratory arrest induced by hanging." Resuscitation 2005;67:143–4. "Neurologically uneventful 2 hanging cases." Med J Niigata City General Hospital 2015;36(1)), suggesting the need for further accumulation of subjects to select indicated victims for TTM.

Keywords Cardiac arrest due to suffocation/hanging · TTM (targeted temperature management) · pH at admission (arrival) · Bystander CPR

4.1 Introduction

According to the 2015 JRC (Japan Resuscitation Council) guidelines for cardiopulmonary resuscitation, TTM (targeted temperature management) at a temperature level choosing from 32 to 36 °C is recommended for patients in a coma after cardiac arrest. However, the cause of cardiac arrest and the time required for spontaneous circulation to return may possibly affect the outcome. For inpatients after cardiac arrest even without VF/pVT, shockable rhythms (2015 JRC treatment recommendation: We suggest. Level of evidence: very low) are indicated for TTM. However, it is unclear whether TTM should be carried out for outpatients who suffered airway obstruction due to foreign body aspiration or hanging.

4.2 Objective

Patients in a state of post-cardiac arrest due to suffocation or hanging may not have improved prognoses even after undergoing targeted temperature management (TTM). Therefore, to obtain characteristics of such patients, we retrospectively evaluated patients' data including other pathologies.

4.3 Methods

We retrospectively evaluated 60 patients who suffered cardiopulmonary arrest inside or outside our hospital and received TTM from June 2009 to July 2016. They were divided into the two groups for parameter comparisons: CPC1–CPC2 and CPC3–CPC5 at hospital discharge. JMP7.0 was used for statistical analysis, while the Wilcoxon rank sum test and χ^2 test were used for testing statistical significance. Data were shown in mean ± SD. **Depicted as statistical significance. **CPC*

cerebral performance categories; outcome of brain-injured patients: the Glasgow-Pittsburgh cerebral performance and overall performance categories.

4.4 Results

As shown in Fig. 4.1, 40 male and 20 female subjects were included in this study. The classification of diseases is given in Fig. 4.2: patients with acute myocardial infarction made up the majority of 33.3%, while the rate of patients suffered suffocation or hanging was 15%. TTM was carried out in all cases of this study.

Table 4.1 showed the comparisons in parameters between the groups of CPC1–CPC2 and CPC3–CPC5 in all 60 cases. Table 4.2 described the comparison between the groups of suffocation/hanging and cardiac arrests from other origins.

Tables 4.3 and 4.4 demonstrated the demographic data of the suffocating cases (abbreviations: FBO, foreign body obstruction; ROSC, return of spontaneous circulation).

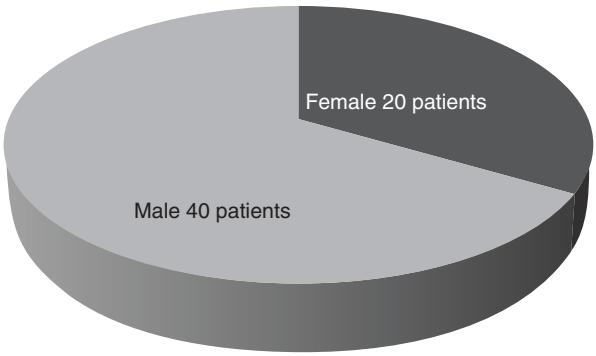


Fig. 4.1 TTM was carried out in all cases of this study. The number of males and females are shown

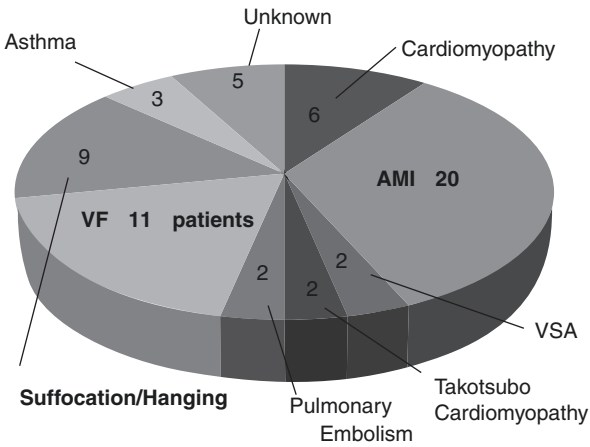


Fig. 4.2 **VSA* vasospastic angina. Patients with acute myocardial infarction accounted for the majority, at 33.3%, while 15% suffered suffocation or hanging

Table 4.1 Comparison between the CPC1–CPC2 and CPC3–CPC5 groups of the overall 60 cases

	CPC1–CPC2	CPC3–CPC5	*P* value
N	16	44	
Gender (male/female)	13:3	27:17	n.s.
Age	63.9 ± 12.7	64.1 ± 16.0	n.s.
BMI	26.9 ± 3.9	24.5 ± 4.1	n.s
Hospitalization duration	34.6 ± 28.4	55.7 ± 68.0	n.s.
pH	7.12 ± 0.18	6.94 ± 0.18	$p = 0.0027$*
HCO_3^- (mEq/L)	19.17 ± 5.42	17.99 ± 6.56	n.s.
B.E. (mEq/L)	−10.76 ± 6.29	−14.76 ± 7.00	$p = 0.026$*
K (mEq/L)	4.50 ± 0.96	4.74 ± 1.20	n.s.
Suffocation/hanging or others	0:16	9:35	$p = 0.0497$**
Witnessed by others: yes/no	15:1	34:10	n.s.
With or without bystander CPR	13:3	31:13	n.s.
With or without PCPS	3:13	5:39	n.s.

Data were shown in mean ± SD. *Wilcoxon rank sum test and **χ^2 test

Table 4.2 Comparison between the suffocation/hanging group and the group suffering cardiac arrest due to other diseases

	Hanging/suffocation	Others	*P* value
N	9	51	
Gender (male/female)	5:4	35:16	n.s.
Age	55.8 ± 18.6	65.5 ± 14.1	n.s.
BMI	22.5 ± 1.8	25.4 ± 4.1	n.s
Hospitalization duration (day)	29.6 ± 22.6	52.0 ± 63.9	n.s.
pH	6.83 ± 0.09	7.02 ± 0.19	$p = 0.0058$*
HCO_3^- (mEq/L)	13.44 ± 4.42	19.16 ± 6.17	$p = 0.0102$*
B.E. (mEq/L)	−19.49 ± 3.08	−12.67 ± 7.01	$p = 0.0031$*
K(mEq/L)	4.66 ± 1.41	4.68 ± 1.10	n.s.
Witnessed: yes/no	3:6 (33.3%:66.7%)	46:5 (90.2%:9.8%)	$p = 0.0006$**
Bystander CPR with or without	4:5 (44.4%:55.6%)	40:11 (78.4%:21.6%)	$p = 0.0481$**

Data were shown in mean ± SD. *Wilcoxon rank sum test and **χ^2 test

Table 4.3 List of patients who suffered airway obstruction due to foreign body aspiration or hanging

Sex	Age	Witness	Bystander CPR	Cause	State of arrival	Admission temperature (°C)
F	38	No	Yes	Hanging	Asystole	36.4
M	82	Yes	Yes	FBO	Asystole	36.9
M	35	No	No	FBO	Asystole	36.6
M	58	No	No	FBO	ROSC	38.9
F	77	No	Yes	FBO	Asystole	34.5
F	55	No	Yes	Hanging	ROSC	35.2
M	76	Yes	No	FBO	Asystole	35.8
M	40	No	No	Hanging	Asystole	36
F	41	No	No	Hanging	PEA	36.6

FBO foreign body obstruction; *ROSC* return of spontaneous circulation

Table 4.4 List of patients who suffered from airway obstruction due to foreign body aspiration or hanging

Sex	Age	Duration until ROSC after arrival at hospital	Achieving time of TIM (34 °C)	Highest body temperature (°C) within 48 h after arrival	Outcome
F	38	In 6 min	In 90 min	34	CPC5
M	82	In 8 min	In 155 min	36.9	CPC5
M	35	In 3 min	In 161 min	36	CPC4
M	58	ROSC before arrival	In 30 h	38.9	CPC4
F	77	In 30 min	In 17 h	38	CPC5
F	55	ROSC before arrival	In 3 h and 44 min	38.2	CPC5
M	76	In 10 min	In 2 h and 43 min	36.6	CPC5
M	40	In 12 min	In 5 h and 37 min	36.8	CPC5
F	41	ROSC before arrival	In 3 h and 52 min	37.8	CPC5

4.5 Case Reports

4.5.1 Case 1. Age: 38 Female Hanging

The patient had been regularly visiting the Department of Psychosomatic Medicine for depression for 10 years. She was found unconscious at home by a family member 5 min after a sound was heard. An emergency service team received a call and transported the patient to hospital in 18 min. With a bystander CPR, adrenaline 2 mg resulted in the resumption of heartbeat. Upon arrival in the ER, light reflex was observed with both pupils having a diameter of 3.5 mm. Her body temperature was 36.4 °C; blood gas analysis showed that pH 6.675, B.E. −25.6 mEq/L, HCO_3 13.5 mmol/L, PCO_2 118.5 Torr, PO_2 62 Torr, and K 6.1 mEq/L. GOT 155 IU/L GPT 185 IU/L. LDH 410 IU/L. CPK 100 IU/L. Her outcome was CPC5 on day 74 after pseudomonas aeruginosa septicemia.

4.5.2 Case 2. Age: 82 Male Foreign Body Aspiration During Alcohol Intoxication

The patient suffered from foreign body aspiration twice, resulting in CAP, followed by a bystander CPR and then was transferred with continued CPR to a hospital by an ambulance. It took 27 min for transportation to the hospital. Upon arrival, no light reflex was observed with pupil diameters of rt. 4 mm/left 5 mm. Upon arrival, his body temperature was 36.9 °C. Blood gas analysis showed that pH 6.915, B.E. −13.9 mEq/L, HCO_3 21.4 mmol/L, PCO_2 107.8 Torr. PO_2 1.2 Torr, K 6.6 mEq/L, GOT 61 IU/L, GPT 34 IU/L, LDH 314 IU/L, and CPK 78 IU/L. Blood ethanol level: 172.0 mg/dL. His outcome was CPC4, eventually, CPC5 with DNAR on day 16.

4.5.3 *Case 3. Age: 58 Male Foreign Body Aspiration from During Eating Meat and Alcohol Drinking*

The patient had a history of smoking but no particular disease history. While eating and drinking at a steak house, he choked on a piece of meat, resulting in cardiac arrest. He did not receive bystander CPR at the site. At 1:23, PEA was confirmed. At 1:24, his heartbeat resumed after sternal compressions. A 6 cm piece of meat was removed. E1VTM2. Within a period of 24 h, his maximum body temperature was 38.9 °C. It took 24 min for the emergency team to transport the patient to the hospital after receiving the call. Pupil diameter: 1.5 (+)/1.5 (+). Upon arrival, his blood gas analysis showed that pH 6.922, B.E. −17.5 mEq/L, HCO_3 17.4 mmol/L, PCO_2 86.4 Torr, PO_2 250.6 Torr, K 3.2 mEq/L, GOT 46 IU/L, GPT 30 IU/L, LDH 279 IU/L, and CPK 276 IU/L. Blood ethanol concentration was 266.2 mg/dL. His outcome was intractable myoclonic epilepsy being difficult to treat. We could not stop his epileptic seizures using anti-epilepsy medicine alone and could not evaluate his consciousness level accurately for a long time due to the use of sedative agents. He was transferred to another hospital on day 56.

4.5.4 *Analysis of Suffocating Cases*

The mean ambulance transportation time was 22.8 ± 3.76 min. Two cases were witnessed. The four patients received bystander CPR (Table 4.3). Spontaneous heartbeats in three cases resumed before reaching the hospital (Table 4.4). The average time until ROSC was 34.8 ± 8.53 min. All 9 patients suffering from airway obstruction or hanging were evaluated as poor outcome (CPC3–CPC5), while 16 out of 51 patients showed neurologically favorable outcomes (CPC1–CPC2) ($p = 0.0497$) (Table 4.1). The cases of hanging were mostly suffering from psychosomatic medical diseases (five cases), while cases of airway obstruction due to foreign body aspiration were those who had drunk a considerable amount of alcohol (three cases). Nielsen et al. [1] showed that there were differences in the TTM management procedures depending on attending physicians in ICU at the time of arrival, and in some cases, it took 30 h to get 34 °C targeted temperature. In our hospital, there is a variety of doctors on shift duty including heart surgeons, cardiologists or nephrologists, which might be a cause of delayed induction for TTM.

4.6 Discussion

The present results suggest that TTM might not be able to improve the outcomes of patients who suffered from airway obstruction due to foreign body aspiration or hanging.

Case 3 in this report had a high fever of 38.9 °C upon arrival. If TTM had been initiated in the early stage, myoclonus epilepsy might not have been so difficult to treat [2–8]. Possibly it might cause abrupt sympathetic hyperactivity after the insult [9, 10]. In this case, we did not perform TTM because of patient's family intension. The final prognosis might be influenced by the decision for the treatment by patient families' intension based on the underlying diseases or explanations of attending physicians. Certain hospitals do not introduce TTM for patients suffering from airway obstruction due to the foreign body aspiration or hanging. However, improved prognoses have been reported in some studies. Murata et al. reported on a 16-year-old boy who suffered incomplete hanging (some part of the body is touching the ground) and cardiac arrest for 18 min without bystander CPR, but eventually he was discharged with CPC2 [11]. His initial rhythm was VF, and his heartbeat was restarted by the defibrillation using AED. Spontaneous respiration regained during transportation. He had GCS 3 upon arrival at the emergency department. Both pupil diameters were 2.5 mm with no light reflex. His body temperature was 34 °C. So, he was undergoing TTM for 24 h at 34 °C and then was rewarmed to 36 °C for 48 h after the insult. From day 24, he had a sustained fever up to 38–39 °C, and consciousness disturbance continued. Since NSAIDs or others were ineffective in decreasing his fever, on day 49, amantadine 150 mg/day was administered for the purpose of activating the patient activity. The patient recovered gradually to a state such that he could look after himself on day 56. Thus, even some cardiac arrest victims after hanging might recover at CPC1 or CPC2. Therefore, in the future, we need to establish the neuromonitoring for evaluating the brain function even in the early phase of post-cardiac arrest for selecting the right victims to be treated.

Ola et al. reported on the outcomes of cases of near hanging treated in two ICUs in Sweden from 2003 to 2006 [12]. Among a total of 13 cases of near hanging, 10 cases did not go into cardiac arrest. Five patients who underwent TTM treatment and all three patients who did not receive TTM were discharged with CPC1–CPC2. Interestingly, only one patient of three subjects in cardiac arrest who received TTM was discharged with CPC1–CPC2. The most important outcome predictors after near hanging were suspension time, depth of coma, and whether or not CA had occurred. The estimated cardiac arrest time of our cases was for 24–56 min (an average duration, 34.8 min). The good recovery case was reported to have a short cardiac arrest time (as described in the paper of Kashif M et al. 15 min [13]) and also with the initial wave form VF (relatively short time expecting with a little damage to the heart), the cases without comorbidities with good overall status. But in the present study, there were no VF forms as the initial wave at the site. The initial wave form VF could be expected to be correlated with a good outcome, so even a hanging case may be an indication of TTM if fulfilled the conditions stated above [12].

Baldursdottir et al. have reported 14 cardiac arrest cases due to hanging and suffocation including carbon monoxide poisoning and drowning. Among them, six cases of cardiac arrests due to hanging underwent TTM: three of the patients were discharged from the hospital at CPC1. The pHs of the patients on admission were 7.31, 7.38, and 7.27, respectively [14].

Jung Hee Wee et al. examined 111 cardiac arrest cases admitted from January 1, 2007 to December 31, 2012. The average age of the patients was 65.8 ± 16.3, with

70.3% of cases suffering cardiac arrest due to clogging of the airway with a foreign body. All patients underwent TTM at 32–34 °C, among 52 patients survived, and 6 of them were discharged with CPC1–CPC2. Light reflex, corneal reflex, and time to ROSC were reportedly to be potential predictors for survival [15].

Min Joung Kim et al. demonstrated that among 159 patients who suffered hanging but were not in cardiac arrest, 12 cases of CPC3–CPC5 did not receive TTM, suggesting that TTM might have led to different results depending on each patient condition. As characteristics of the hanging cases with cardiac arrest who received TTM getting CPC1–CPC2, the authors reported the following: (1) CPR time before hospital transfer was short as approximately 5 min; (2) pH was greater than 7.28; (3) the base excess was higher than −4.7 mEq/L; and (4) HCO_3^- was greater than 20.5 mEq/L. pH and HCO_3^- could be useful as prognostic predictors; in our study, all cases had a pH less than 7.0 [16].

Two cases of hanging who were not in cardiac arrest were reported. A patient was a 40-year-old male with E1V2M4, and his bladder temperature was 39.0 °C on admission. He received TTM management and was discharged on the 52nd day with CPC1. Although the other patient was discovered in a state of his left foot submerging 2 m under the floor, he was rescued by family members to recover both respiration and circulation when emergency personnel arrived. Upon arrival at the emergency department, the patient was E2V2M4 with an axillary temperature of 36.4 °C and received TTM; eventually he regained his consciousness even before discharge with CPC1 on the 14th day [17].

In some cases, there were actually no cardiac arrests in a group who were thought to have cardiac arrest. According to the home page for citizens by the Japanese Circulation Society (http://www.j-circ.or.jp/cpr/call.html), confirmation of a pulse is not required. It is recommended to compress the chest if there is no consciousness nor respiration. Therefore, some patients who suffered airway obstruction from foreign body aspiration or hanging might not experience cardiac arrest, but cerebral hypoxia could occur, so TTM should not suspend for cases of airway obstruction such from hanging. Patients who do not respond to verbal command after cardiac arrest are indicated for TTM. Cooling starts earlier; less brain damage could be expected [18]. We had a drowned woman of 50s with cardiac arrest: her pH was 6.94, the duration of arrest was approximately 40 min, but her body temperature on arrival was 34.4 °C. After 4 days, she was discharged with CPC1 [19]. In this study, no cases had a body temperature around 34 °C on admission (Table 4.3).

The mechanisms of cardiac arrest due to airway obstruction caused by foreign body aspiration or hanging may vary. Suzutani et al. reported that the mechanisms of cardiac arrest due to hanging are as follows: (1) obstruction of the airway; in typical dead cases by hanging, the base part of the tongue is pushed back and upward and tightly adhered to the posterior pharyngeal wall, resulting in closure of the airway at the pharynx part (external suffocation); (2) obstruction of the cervical blood vessels, wherein the cervical blood vessels are externally compressed by hanging and their lumens are collapsed, blood circulation to the cranial cavity instantaneously stops, and then oxygen deficiency occurs in the brain (internal suffocation); (3) compression of the cervical nerve; and (4) cervical vertebral fracture and transec-

tion of the neck or a combination of them. The simultaneous occurrence of (3) and (4) is reported to be rare [20]. In this study, there were no cases involving the mechanism (4). If either (1) or (2) occurs, oxygen is not delivered to the brain. Therefore, they are causes of cardiac arrest due to hypoxic mechanisms. In the current cases whose ROSC could not be obtained, PCO_2 levels were over 110 Torr, so it is likely that they are a group of inadequate ventilation.

4.6.1 Study Limitation

This study was a retrospective evaluation at a single facility. One of the causes for cardiac arrest from suffocation and airway obstruction is hypoxemia, while the mechanism of cardiac arrest in hanging cases may be due to internal/external suffocation, cervical nerve compression, or carotid sinus/vagal activations; thus there would be complication. Therefore, it is possible that the mechanisms of cardiac arrest may vary among cases suffering from airway obstruction due to foreign body aspiration or hanging leading to cardiac arrest.

4.7 Conclusions

Patients who suffered from airway obstruction due to foreign body aspiration or hanging without cardiac arrest are reported to mostly recover to CPC1–CPC2. However, in some cases on arrival, it is difficult to determine whether such patients did have cardiac arrest or not. In such situation, pH upon arrival, at least in part, might offer information regarding the possibility of cardiac arrest, thereby potentially predicting prognoses. TTM might have reduced brain damage after cardiac arrest due to suffocation mechanisms. However, since there has been very limited evidence, we could neither recommend nor refute TTM for post-cardiac arrest patients after suffocation. Therefore, we need to accumulate more data and elaborate to allow us to determine subjects who would recover to neurologically favorable outcomes.

Acknowledgments The authors have no conflicts of interest directly relevant to the content of this article.

References

1. Nielsen N, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med. 2013;369(23):2197–206.
2. Liu Z, et al. Effect of temperature on kainic acid-induced seizures. Brain Res. 1993;17(631):51–8.

3. Jiang W, et al. The neuropathology of hyperthermic seizures in the rat. Epilepsia. 1999;40:5–19.
4. Lundgren J, et al. Hyperthermia aggravates and hypothermia ameliorates epileptic brain damage. Exp Brain Res. 1994;99:43–55.
5. Wang Y, et al. Hypothermia reduces brain edema, spontaneous recurrent seizure attack, and learning memory deficits in the kainic acid treated rats. CNS Neurosci Ther. 2011;17:271–80.
6. Maeda T, et al. Effect of hypothermia on kainic acid-induced limbic seizures: an electro-encephalographic and 14C-deoxyglucose autoradiographic study. Brain Res. 1999;13(818):228–35.
7. Schmitt FC, et al. Anticonvulsant properties of hypothermia in experimental status epilepticus. Neurobiol Dis. 2006;23:689–96.
8. Kowski AB, et al. Deep hypothermia terminates status epilepticus—an experimental study. Brain Res. 2012;29(1446):119–26.
9. Rabinstein AA. Paroxysmal sympathetic hyperactivity in the neurological intensive care unit. Neurol Res. 2007;29:680–2.
10. Perkes I, Baguley IJ, Nott MT, et al. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. Ann Neurol. 2010;68:126–35.
11. Murata Y, et al. A patient who received amantadine for consciousness disturbance after cardiac arrest/heartbeat resumption by hanging. Jpn Soc Intensive Care Med. 2015;22:536–9.
12. Borgquist O, et al. Therapeutic hypothermia for comatose survivors after near-hanging-a retrospective analysis. Resuscitation. 2009;80(2):210–2.
13. Kashif M, et al. Early recognition of foreign body aspiration as the cause of cardiac arrest. Case Rep Crit Care. 2016;2016:1329234.
14. Baldursdottir S, et al. Induced hypothermia in comatose survivors of asphyxia: a case series of 14 consecutive cases. Acta Anaesthesiol Scand. 2010;54(7):821–6.
15. Wee JH, et al. Outcomes of asphyxia cardiac arrest patients who were treated with therapeutic hypothermia: a multicentre retrospective cohort study. Resuscitation. 2015;89:81–5.
16. Kim MJ, et al. Neurologic outcome of comatose survivors after hanging: a retrospective multicenter study. Am J Emerg Med. 2016;34(8):1467–72.
17. Aso Y. Two cases of hanging who got back into society. Med J Niigata City General Hospital. 2015;36(1):86–7.
18. Brian EG, et al. Targeted temperature management after out-of-hospital cardiac arrest: who, when, why, and how? Can Fam Physician. 2015;61(2):129–34.
19. Nagama M, et al. A patient who drowned at sea and suffered hypothermia with bystander CPR but was able to re-enter society without aftereffects. Jpn Assoc Acute Med. 2017:170.
20. Suzutani T. Discussion on the mechanisms and causes of death by hanging. Hokkaido J Med Sci. 1982;57(5):642–8.

Chapter 5
Prediction in Neurological Outcomes in Cardiac Arrest Patients Before Inducing Targeted Temperature Management: Validation of CAST or cCAST

Mitsuaki Nishikimi

Abstract Not only a patient's family but also ICU physicians need information on the probability of a patient recovering from post-cardiac arrest syndrome (PCAS) before admitting to the intensive care unit (ICU) and initiating targeted temperature management (TTM). In this section, we introduced a novel prediction tool for evaluating the neurological prognosis in patients with PCAS before TTM, called a post-Cardiac Arrest Syndrome for Therapeutic hypothermia score (CAST) and condensed CAST (cCAST). They have been developed using retrospective analyses from data of 151 consecutive adult patients who were admitted to four hospitals within the last 5 years to undergo TTM after cardiac arrest. While the CAST was calculated by using eight factors and logistic regression formula, the cCAST was modified by, though using same factors, more simple formula. The cCAST of 3.5 or lower was associated with a 0.99 (95% CI, 0.94–1.00) sensitivity and a 0.73 (0.61–0.84) specificity predicting for a poor outcome and 6.5 or higher was with a 0.80 (0.71–0.88) and a 0.97 (0.89–1.00). The "cCAST" can be calculated more easily and is useful for estimating the prognosis of PCAS patients, describing patients' conditions to their family and making the decision before the initiation of TTM, as with the original CAST.

Keywords Post-cardiac arrest syndrome · Neurological prognosis · Targeted temperature management · CAST · cCAST

M. Nishikimi
Department of Emergency and Critical Care, Nagoya University Graduate School of Medicine, Nagoya, Japan

M. Aibiki, S. Yamashita (eds.), *A Perspective on Post-Cardiac Arrest Syndrome*,
https://doi.org/10.1007/978-981-13-1099-7_5

Abbreviations

95% CI	95% confidence interval
CAST	Post-cardiac arrest syndrome for therapeutic hypothermia score
cCAST	condensed CAST
CPC	Cerebral performance categories
ED	Emergency department
GCS	Glasgow Coma Scale
GWR	Gray matter attenuation to white matter attenuation ratio
ICU	Intensive care unit
PCAS	Post-cardiac arrest syndrome
TTM	Targeted temperature management

5.1 Introduction

5.1.1 The Estimation of Prognosis of PCAS Before the Initiation of TTM

Cardiac arrest typically occurs suddenly, and the families of patients are often confused on resuscitation and return of spontaneous circulation in the emergency department (ED). Objective information regarding recovery might be helpful to explain the patient's current status to his or her family clearly. Moreover, such information could also be helpful for the intensive care unit (ICU) physicians from the viewpoint of cost-effectiveness, because the cost of critical care for them is usually exorbitant, so the indications for the treatment in post-cardiac arrest syndrome (PCAS) patients should be decided more carefully [1]. Estimating the neurological prognosis immediately after the return of spontaneous circulation is challenging but important for the treatment of patients after cardiac arrest.

Previous studies have examined several factors that are available at the emergency department (ED) before the initiation of targeted temperature management (TTM) to determine their relation to the neurological prognosis of PCAS patients. For example, the duration of the resuscitation effort was shown to be correlated with a good functional outcome for patients with PCAS [2, 3]. In addition, other studies have revealed that pH [4], lactate [5, 6], and the Glasgow Coma Scale (GCS) [7, 8] are also related to neurological prognosis. However, these factors could not sufficiently separate patients with a good outcome from those with a poor outcome, indicating that a more "suitable scaling method" based on a combination of prognostic factors would be needed [9, 10].

Although several studies have described the use of a scoring system to estimate neurological outcome on the patient's arrival in the ED, these scoring systems did not focus on whether the patient had undergone TTM [4, 11–13]. Today, many intensivists perform TTM for the purpose of promoting a good recovery if intensive treatment is indicated. Logically, a scoring system for PCAS patients undergoing

TTM should be created using data from only PCAS patients treated with TTM, but not from all PCAS patients. Moreover, the factors used for these previous scoring systems were mostly limited to clinical history items, such as the time until ROSC, the initial rhythm, and the witness status. Potential candidate values used on their creation were not selected from blood and physical examination findings or imaging studies. If the scoring system for predicting the outcome of the PCAS patients is developed by the limited data of those undergoing TTM, furthermore the data including the other examinations such as blood and physical examination findings or imaging studies as well as clinical history, it is likely to be more suitable scoring system for them.

5.1.2 *Post–Cardiac Arrest Syndrome for Therapeutic Hypothermia Score (CAST)*

Previously, we developed a "post-Cardiac Arrest Syndrome for Therapeutic hypothermia score (CAST)" for predicting the neurological outcome in patients with PCAS before the initiation of TTM [14, 15]. CAST was created in a multicenter, retrospective, observational study using a data of 151 adults who were admitted to four hospitals within the last 5 years to undergo TTM after cardiac arrest. It is calculated using eight categorized variables (initial rhythm, witnessed status and time until return of spontaneous circulation, pH, serum lactate, motor score according to the Glasgow Coma Scale, CT gray matter to white matter attenuation ratio, albumin, hemoglobin), which was strongly associated with neurological prognosis of PCAS patients at 30 days, and logistic regression formula (Figs. 5.1 and 5.2). The predictive accuracy of CAST has much higher as compared with previous reported scoring

Scrore	*0*	*1*	*2*	*3*
Initial Rhythm (X1)	*Shockable*	*Non Shockable*		
Witness / ROSC time (X2)	*< 20 min*	*20 min ≤*	*No Witness*	
pH (X3)	*≥ 7.31*	*7.30-7.16*	*7.15-7.01*	*7.00 ≥*
Lactate (X4)	*≤ 5.0*	*5.1-10.0*	*10.1-14.0*	*14.1 ≤*
GCS M (X5)	*≥ 2*	*1*		
GWR (X6)	*≥ 1.201*	*1.200-1.151*	*1.150 ≥*	
Alb (X7)	*≥ 3.6*	*3.5-3.1*	*3.0 ≥*	
Hb (X8)	*≥ 13.1*	*13.0-11.1*	*11.0 ≥*	

Fig. 5.1 The categorical classification of eight variables. *ROSC time* time until return of spontaneous circulation; *GCS M* motor scale according to Glasgow Coma Scale; *GWR* gray matter to white matter attenuation ratio; *Alb* albumin; *Hb* hemoglobin. This figure was cited from a figure of Nishikimi's article [14]

a

	Correlation Coefficient
Initial Rhythm	*0.570 (a1)*
Witness / ROSC time	*1.040 (a2)*
pH	*1.167 (a3)*
Lactate	*0.338 (a4)*
GCS M	*2.225 (a5)*
GWR	*1.480 (a6)*
Alb	*1.077 (a7)*
Hb	*0.595 (a8)*
intercept	*-5.282 (a9)*

b

Scrore (A) = a1 x X1+a2 x X2 ...+a9

a: correlation coefficient
X: categorized variables in Fig.5.1

$$\text{Probability For Good Outcome} = \frac{(e^{-A})}{1 + (e^{-A})}$$

Fig. 5.2 Calculation used for the *post-Cardiac Arrest Syndrome for Therapeutic hypothermia score* (*CAST*). Using the categorical classification of eight variables (Fig. 5.1) and the correlation coefficients for the data (**a**), the resulting scores and probability of a good outcome were calculated (**b**). *ROSC time* time until return of spontaneous circulation; *GCS M* motor scale according to Glasgow Coma Scale; *GWR* gray matter to white matter attenuation ratio; *Alb* albumin; *Hb* hemoglobin. This figure was cited from a figure of Nishikimi's article [14] (partially modified)

system for PCAS [4, 12], but the calculation was a little complex. It needs some electronic devices for the calculation [16, 17]. Simplified version of CAST, which can be calculated more easily but has similar predictive accuracy, may be needed. Thus, the aim of this study is to develop the simplified version of the original CAST, which can calculate in an easier manner, condensed CAST (cCAST).

5.2 Methods

5.2.1 Study Design

A multicenter, retrospective, observational study was performed. The same patients' data had been retrospectively analyzed for developing the original score. A data of 151 adults who were admitted to four hospitals within the last 3–5 years to undergo TTM after cardiac arrest was reanalyzed: 54 patients treated at Nagoya University Hospital between April 2011 and March 2016, 23 patients treated at Chutouen General Medical Center between April 2013 and March 2016, 64 patients treated at Japan Red Cross Maebashi Hospital between April 2011 and March 2016, and ten patients treated at Komaki City General Hospital between April 2012 and March 2016. Eligible patients were all PCAS patients who were treated with TTM. They were excluded if they were traumatic cardiac arrest patients, or pediatric patients (age <18 years), or did not have lived independently prior to experiencing cardiac arrest.

5.2.2 Participating Hospital

The four participating hospitals are all tertiary emergency medical centers (Japanese centers for emergency patients with serious or life-threatening conditions): Nagoya University Hospital is an academic hospital; and Chutouen General Medical Center, Japan Red Cross Maebashi Hospital, and Komaki City General Hospital are general hospitals. Nagoya University Hospital and Japan Red Cross Maebashi Hospital are both located in a city and have 1035 and 592 beds each, including 26 and 12 ICU beds, respectively; these hospitals, respectively, treat about 12,000 and 20,000 emergency patients each year. Chutouen General Medical Center and Komaki City General Hospital are both located in the countryside and have 500 and 558 beds each, including 10 and 30 ICU/CCU beds; these hospitals treats about 20,000 and 30,000 emergency patients per year.

5.2.3 Data Set

Data was collected retrospectively from electronic chart reviews, including the clinical histories (age, sex, situation surrounding the cardiac arrest), cardiac rhythms, physical examinations (GCS, mydriasis), results of blood examinations (C-reactive protein [CRP], albumin [Alb], hemoglobin [Hb], glucose, creatinine, pH, lactate), cranial CT scan images, and clinical courses after admission. The gray matter attenuation to white matter attenuation ratio (GWR) was measured using the method described in previous report [15]. Physical examination was obtained just after return of spontaneous circulation, and results of blood examinations were obtained about 15 min before and after return of spontaneous circulation. CT scan images were obtained using an Aquilion64 (TOSHIBA) or SOMATOM Definition Flash (SIEMENS) within 6 h after the patient's cardiac arrest event.

5.2.4 Protocol of TTM

TTM was considered for cardiac arrest patients who were in a coma (GCS $\leq$8) after ROSC without remarkable hemodynamic instability or a "Do Not Attempt to Resuscitation" directive. A temperature between 34 and 36 °C was targeted by the infusion of cold fluids in combination with surface cooling, an ice pack and cold blanket, or a surface cooling device with a computerized automatic temperature control (Arctic Sun 2000 TTM; Bard Medical Louisville, CO). After the targeted temperature had been maintained for 24 h, rewarming to 36 °C was performed at a rate of 0.2 °C/4 h. Propofol, dexmedetomidine, midazolam, fentanyl, and rocuronium were used for sedation, analgesia, and muscle relaxation according to individual clinician preferences. At all the participating hospitals,

the ventilator settings, fluid infusion, and doses of vasopressors, sedatives, and analgesics were adjusted so that the mean arterial pressure, pCO_2, and urine output were ≥80 mmHg, 35–45 mmHg, and ≥ 0.5 mL/kg/h, respectively, to maintain cerebral perfusion.

5.2.5 Neurological Outcome

We used the cerebral performance categories (CPC) at 30 days to estimate the neurological outcomes as with the original score [18]. The categories were grouped into either a good outcome (1–2) or a poor outcome (3–5).

5.2.6 Statistical Analysis

The statistical method for the development of CAST was shown in our previous study [15]. R software was used for all the statistical analyses.

5.3 Results

5.3.1 Simplified Version of CAST: Condensed CAST (cCAST)

The eight variables (initial rhythm, witnessed status and time until return of spontaneous circulation, pH, serum lactate, motor score according to the Glasgow Coma Scale, gray matter to white matter attenuation ratio, albumin, hemoglobin) on the original CAST were used for the development of cCAST, and the categorization was also performed as with the original (Fig. 5.1). First, the coefficients of the eight items in the cCAST were created by simplifying the correlation coefficients in the logistic regression analysis used for the original (initial rhythm, 0.570, was converted to 0.5; witnessed status and time until return of spontaneous circulation, 1.040 to 1.0; pH, 1.167 to 1.0; serum lactate, 0.338 to 0.5; motor score according to the Glasgow Coma Scale, 2.225 to 2.0; gray matter to white matter attenuation ratio, 1.480 to 1.5; albumin, 1.077 to 1.0; hemoglobin, 0.595 to 0.5). By using the simplified correlation coefficients and categorized variables, the cCAST has been developed (Fig. 5.3). If the score point is high, the probability of PCAS prognosis is poor, and if the score point is low, the probability is good.

Next, for the classification of cCAST, we created the scatter diagram using the all data (Fig. 5.4). Looking at this, we considered we could classify the prognosis most clearly when we set the threshold to 4 and 6. A cCAST of 3.5 or lower was associated with a 0.99 (95% CI, 0.94–1.00) sensitivity and a 0.73

	Correlation Coefficient		Simplified Correlation Coefficient
Initial rhythm	0.570		0.5
Witness/ ROSC time	1.077		1.0
pH	1.167		1.0
Lactate	0.338		0.5
GCS M	2.225		2.0
GWR	1.480	Simplify	1.5
Alb	1.077		1.0
Hb	0.595		0.5

Score points on cCAST = 0.5 *XI* + *X2* + *X3* + 0.5 *X4* + 2 *X5* + 1.5 *X6* + *X7* + 0.5 *X8*

X: categorized variables in Fig.5.1

Fig. 5.3 The method to simplify the original CAST. The correlation coefficients in the logistic regression analysis used for the original CAST was simplified for the development of condensed CAST as shown in the figure. By using the simplified correlation coefficients and categorized variables, the cCAST has been developed. *ROSC time* time until return of spontaneous circulation; *GCS M* motor scale according to Glasgow Coma Scale; *GWR* gray matter to white matter attenuation ratio; *Alb* albumin; *Hb* hemoglobin

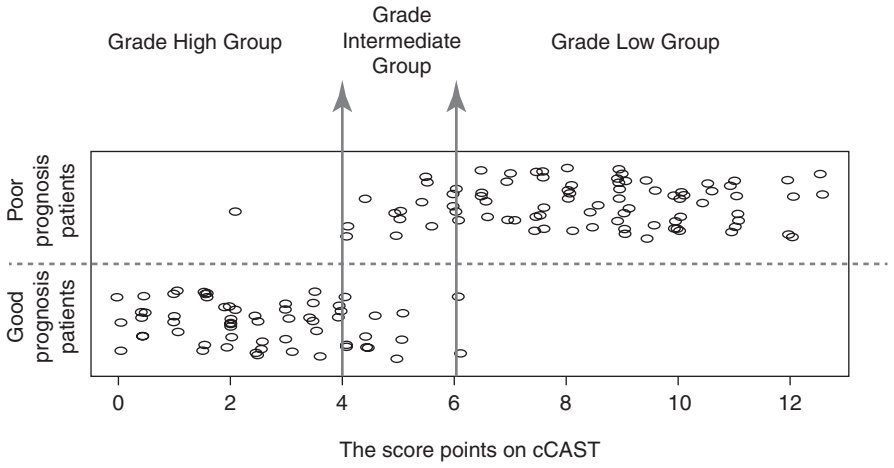


Fig. 5.4 The scatter diagram of the all analyzed patients showing relationship between their score points on cCAST and their neurological outcomes. Looking at this, we considered we could classify the prognosis the most clearly when we set the threshold to 4 and 6

(0.61–0.84) specificity for a poor outcome, and 6.5 or higher was with a 0.80 (0.71–0.88) and a 0.97 (0.89–1.00). Here, specificity measures the proportion of poor prognosis patients who were correctly identified as such. Using these thresholds, we created three grades in cCAST; Grade High (≤3.5), Grade Intermediate (4–6), and Grade Low (6.5 ≤). The 2% (1/48) of all patients classified into the Grade High group (score ≤3.5), 55% (17/31) into the Grade Intermediate group (4–6), and 97% (70/72) into the Grade Low group (≥ 6.5) showed poor outcomes (Table 5.1).

Table 5.1 The proportion of poor outcome patients in each group

cCAST	Grade	Proportion of poor outcome
≤3.5	High	1/48 (2%)
4–6	Intermediate	17/31 (55%)
6.5 ≤	Low	70/72 (97%)

Data are presented as absolute frequencies with percentages

5.4 Discussion

5.4.1 Clinical Use of cCAST

In this study, we created cCAST, which can estimate the prognosis of PCAS patients before the initiation of TTM without calculator. According to the scoring points, we set three grades: Grade High (≤3.5), Grade Intermediate (4–6), and Grade Low (6.5 ≤). While Grade High and Intermediate showed a certain possibility of recovery to a good outcome, Grade Low did not. Since TTM could increase the overall cost of care for all cardiac arrest survivors, the indications should be decided more carefully. Unfortunately, patients who do not have any likelihood of recovery may not be candidates for the critical care treatment including TTM. Thus, still challenging, it appeared that the PCAS patients who are classified into Grade Low may not be candidates for TTM.

However, we have to take care of the use of this scoring system. Note that it shows only the probability of outcome in a general population, not the precise probability for an individual patient [19]. Although predictive scores can be used to help guide decision-making and risk assessment for individual patients, their results are not absolute. Of course, the final therapeutic strategy should be decided after taking different factors into account (e.g., the results of discussions with family members, the patient's own wishes, the societal ethos, etc.), although the results of the scoring system can be used to guide judgment. Most importantly, a patient's exact neurological prognosis cannot be predicted without making decisive examinations, such as an electroencephalogram [15].

This condensed score can be also calculated using eight clinical parameters that are broadly available before the initiation of TTM. But if this scoring system could be combined with a neurological-specific marker or examination, such as NSE or S-100 or an electroencephalogram, it might be possible to predict patient outcome even more precisely. It would be of great interest to predict the neurological outcomes of PCAS patients using this scoring system and other tests before the initiation of TTM.

5.4.2 A Possibility of Further Simplification of cCAST

In future study, we have a plan for further simplification of cCAST by cutting down the value of GWR from the variables for cCAST. The GWR is one of the strongest tools for objectively measuring to detect the hypoxic encephalopathy, and many

previous studies reported that GWR was beneficial for the estimation of PCAS prognosis [18, 20], but the calculation is a little complex, and the brain CT examination needs to be performed for the calculation. Some hospitals cannot always perform the brain CT examination before the initiation of TTM because of several factors such as shortage of radiology technician during night. If we can create the scoring system without the calculation of GWR, it would become useful for broader population.

5.4.3 Limitation

The predictive accuracy of the CAST and cCAST is limited because they were created using retrospective data, even though its generalizability is likely to be high since it was developed using data from multiple centers. The endpoint used in this study was 30 days. Although the outcome at 30 days has been used in a few studies that have attempted to establish a predictive score for cardiac arrest patients [4, 21], it may be better to set longer-term endpoints such as outcome at 90 days for predicting the future clinical course of the patients more accurately [22]. Further prospective validation of the CAST and cCAST and a study examining the utility of these scores for predicting long-term prognosis would be useful.

5.4.4 A Possibility of the Risk Classification for PCAS Using CAST

Finally, we describe a possibility that the CAST may be used for the risk classification of PCAS. After previous TTM trial showed no effect of therapeutic hypothermia as compared with normothermia [23], the optimal targeted setting temperature during TTM for PCAS remains unclear. One of the possible reasons why the aforementioned study failed to show a beneficial of TTM at lower targeted setting temperature is that the subject population in that study included PCAS patients of all grades, including the highest and lowest grade, of severity. Logically, the effect size of TTM at lower targeted temperature would be expected to differ according to the severity of PCAS, and there may be a group with a particular severity who has more benefit from it. In actual clinical practice, we may feel that if the PCAS patients had several signs for poor prognosis prediction (if their cardiac arrest was no witness, the time until return of spontaneous circulation was over 1 h, and they had the presence of findings of hypoxic encephalopathy in their brain CT), they may remain poor outcome even if they underwent TTM at lower targeted temperature. On the other hand, we may feel that if they had several signs for good prognosis prediction (if their cardiac arrest was with witness and bystander and the time until return of spontaneous circulation was only 1 min), they will show good outcome even if they did not undergo TTM at lower targeted temperature. The group who had most

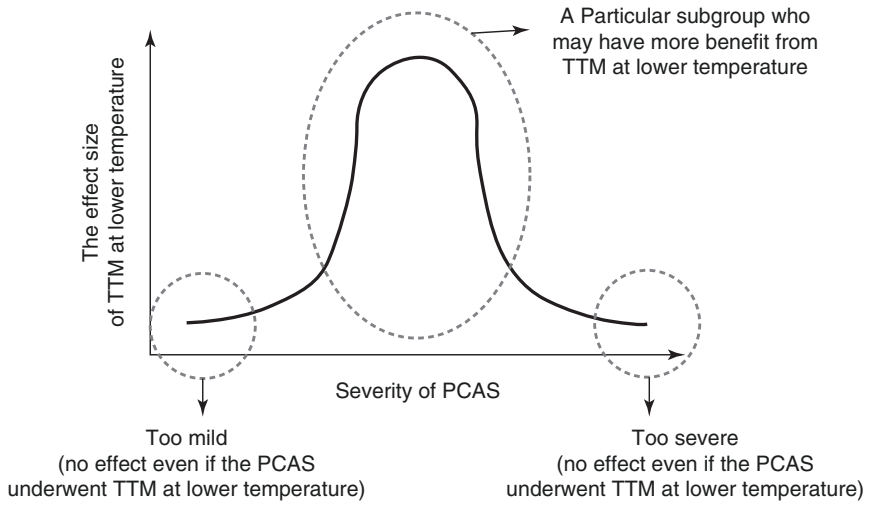


Fig. 5.5 Schema of our hypothesis. The group who had most benefit from TTM at lower targeted temperature may be not too severe and not too mild group, in other words, the intermediate group according to their severity. *TTM* targeted temperature management; *PCAS* post-cardiac arrest syndrome

benefit from TTM at lower targeted temperature may be not too severe and not too mild group, in other words, the intermediate group according to their severity (Fig. 5.5).

Considering that the CAST is the score for predicting the neurological prognosis in PCAS patients before the initiation of TTM, the probability for good prognosis on CAST may be able to be converted to their severity, and it may be also useful for the risk classification of PCAS treated with TTM. For example, the patients who showed poor prognosis on CAST may be regarded as "severe PCAS," and such patients may show a poor outcome regardless of the targeted temperature in TTM. On the other hand, the patients who showed good prognosis on CAST may be regarded as "mild PCAS," and such patients may show a good outcome regardless of the targeted temperature in TTM. Based on our assumption, it would be great interest of investigating the correlation between the targeted setting temperature in TTM and the neurological outcome among the intermediate score group patients on CAST in future study.

5.5 Conclusion

The cCAST can be calculated more easily and is useful for estimating the prognosis of PCAS patients, explaining patients' conditions to their family, and possibly making the decision before the initiation of TTM, as with the original. Further prospective validation of the CAST and cCAST would be needed.

References

1. Gajarski RJ, Smitko K, Despres R, Meden J, Hutton DW. Cost-effectiveness analysis of alternative cooling strategies following cardiac arrest. Springerplus. 2015;4:427.
2. Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? Circulation. 2013;128(23):2488–94.
3. Kaneko T, Kasaoka S, Nakahara T, Sawano H, Tahara Y, Hase M, et al. Effectiveness of lower target temperature therapeutic hypothermia in post-cardiac arrest syndrome patients with a resuscitation interval of </=30 min. J Intensive Care. 2015;3(1):28.
4. Seeger FH, Toenne M, Lehmann R, Ehrlich JR. Simplistic approach to prognosis after cardiopulmonary resuscitation-value of pH and lactate. J Crit Care. 2013;28(3):317 e313–20.
5. Mullner M, Sterz F, Domanovits H, Behringer W, Binder M, Laggner AN. The association between blood lactate concentration on admission, duration of cardiac arrest, and functional neurological recovery in patients resuscitated from ventricular fibrillation. Intensive Care Med. 1997;23(11):1138–43.
6. Kliegel A, Losert H, Sterz F, Holzer M, Zeiner A, Havel C, et al. Serial lactate determinations for prediction of outcome after cardiac arrest. Medicine (Baltimore). 2004;83(5):274–9.
7. Grossestreuer AV, Abella BS, Leary M, Perman SM, Fuchs BD, Kolansky DM, et al. Time to awakening and neurologic outcome in therapeutic hypothermia-treated cardiac arrest patients. Resuscitation. 2013;84(12):1741–6.
8. Golan E, Barrett K, Alali AS, Duggal A, Jichici D, Pinto R, et al. Predicting neurologic outcome after targeted temperature management for cardiac arrest: systematic review and meta-analysis. Crit Care Med. 2014;42(8):1919–30.
9. Young GB. Clinical practice. Neurologic prognosis after cardiac arrest. N Engl J Med. 2009;361(6):605–11.
10. Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med. 2014;42(6):1340–7.
11. Hayakawa K, Tasaki O, Hamasaki T, Sakai T, Shiozaki T, Nakagawa Y, et al. Prognostic indicators and outcome prediction model for patients with return of spontaneous circulation from cardiopulmonary arrest: the Utstein Osaka project. Resuscitation. 2011;82(7):874–80.
12. Goto Y, Maeda T, Goto Y. Decision-tree model for predicting outcomes after out-of-hospital cardiac arrest in the emergency department. Crit Care. 2013;17(4):R133.
13. Adrie C, Cariou A, Mourvillier B, Laurent I, Dabbane H, Hantala F, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J. 2006;27(23):2840–5.
14. Nishikimi M, Matsuda N, Matsui K, Takahashi K, Ejima T, Liu K, et al. CAST: a new score for early prediction of neurological outcomes after cardiac arrest before therapeutic hypothermia with high accuracy. Intensive Care Med. 2016;42(12):2106–7.
15. Nishikimi M, Matsuda N, Matsui K, Takahashi K, Ejima T, Liu K, et al. A novel scoring system for predicting the neurologic prognosis prior to the initiation of induced hypothermia in cases of post-cardiac arrest syndrome: the CAST score. Scand J Trauma Resusc Emerg Med. 2017;25(1):49.
16. CAST for iPad. https://geo.itunes.apple.com/jp/app/meidai-score-for-ipad/id1065338535?mt=8. Accessed 20 Jan 2018.
17. CAST for iPhone. https://geo.itunes.apple.com/jp/app/meidai-score-for-iphone/id1067612773?mt=8. Accessed 20 Jan 2018.
18. Takahashi N, Satou C, Higuchi T, Shiotani M, Maeda H, Hirose Y. Quantitative analysis of brain edema and swelling on early postmortem computed tomography: comparison with antemortem computed tomography. Jpn J Radiol. 2010;28(5):349–54.
19. Nielsen N. Predictive scores, friend or foe for the cardiac arrest patient. Resuscitation. 2012;83(6):669–70.

20. Metter RB, Rittenberger JC, Guyette FX, Callaway CW. Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. Resuscitation. 2011;82(9):1180–5.
21. Aschauer S, Dorffner G, Sterz F, Erdogmus A, Laggner A. A prediction tool for initial out-of-hospital cardiac arrest survivors. Resuscitation. 2014;85(9):1225–31.
22. Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, et al. Primary outcomes for resuscitation science studies: a consensus statement from the American Heart Association. Circulation. 2011;124(19):2158–77.
23. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med. 2013;369(23):2197–206.