Short “infraslow” activity (SISA) with burst suppression in acute anoxic encephalopathy: a rare, specific ominous sign with acute post-hypoxic myoclonus or acute symptomatic seizures

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ABSTRACT

Objective: Slow wave with frequency <0.5 Hz are recorded in various situations such as normal sleep, epileptic seizures. However, its clinical significance has not been fully clarified. Although infraslow activity was recently defined as activity between 0.01 and 0.1Hz, we focus on the activity recorded with time constant of 2 s for practical usage. We defined short "infraslow" activity (SISA) less than 0.5 Hz recorded with time constant of 2 s and investigated the occurrence and clinical significance of SISA in acute anoxic encephalopathy.

Methods: This study evaluated findings of electroencephalography (EEG) in consecutive 98 comatose patients with acute anoxic encephalopathy after cardiac arrest. We first classified EEG findings conventionally, then investigated SISA by time constant of 2 s and a high-cut filter of 120 Hz, to clarify the relationship between SISA and clinical profiles especially of clinical outcomes and occurrence of acute post-hypoxic myoclonus or acute symptomatic seizures.

Results: SISA was found in 6 patients (6.2%), superimposed on the burst phase of the burst-suppression pattern. All 6 patients showed acute post-hypoxic myoclonus or acute

symptomatic seizures (generalized tonic-clonic seizures) and its prognosis was poor. This 100% occurrence of acute post-hypoxic myoclonus or acute symptomatic seizures was significantly higher than that in patients without SISA (39.1%; $P < 0.05$).

Conclusions: SISA in acute anoxic encephalopathy could be associated with acute post-hypoxic myoclonus and acute symptomatic seizures. SISA could be a practically feasible biomarker for myoclonus or seizures and poor prognosis in acute anoxic encephalopathy, if it occurs with burst suppression.

Keywords: short infraslow activity; anoxic encephalopathy; burst-suppression; acute symptomatic seizure

Abbreviations

CPC: Cerebral Performance Category, EEG: electroencephalograms, FFT: fast Fourier transform, SISA: short infraslow activity

1. INTRODUCTION

The outcomes of acute anoxic encephalopathy after cardiac arrest are generally very poor, with only 15-20% achieving good prognosis,[1] and about 50% never regaining consciousness after resuscitation.[2,3] Precise prediction of neurological disabilities or acute symptomatic seizures in these patients is important, since these factors are crucial for the prognosis and decisions of therapeutic intervention. Electroencephalography (EEG) is still one of the most useful examinations in patients with acute anoxic encephalopathy. Background suppression, burst suppression, epileptiform discharges and generalized periodic discharges have been reported as poor prognostic factors.[4,5,6] Clinical manifestations of myoclonic status epilepticus, absence of pupillary light responses, corneal reflexes and motor responses to pain have also been associated with poor outcomes.[4,5] However, the relationships between other patterns on EEG and prognosis or acute symptomatic seizure have not yet been fully clarified.

Very slow EEG activity with frequency <0.5 Hz has been reported in previous studies. The exact generators of this activity remain unknown, but have been presumed

to involve the function of astrocytes,[7] with spontaneous slow oscillating activity of astrocytes seen in an in-vitro study,[8] and voltage differences produced by the function of the blood-brain barrier identified in another study.[9] Some researchers have recorded very slow EEG activity from electrocorticography[10-12] and even from scalp-recorded EEG in epilepsy, brain ischemia and normal sleep.[13,14]

In terms of clinical significance, previous studies have shown that ictal infraslow activity could contribute to delineation of the core epileptogenic area in human intractable epilepsy.[10,11] Another study showed infraslow activity (0.015-0.06 Hz) present in acute anoxic encephalopathy, with larger-amplitude activity only observed in patients with poor outcomes.[15] However, whether such activity emerges in other clinical situations is unclear, and the clinical significance of infraslow activity has not been clarified. In addition, filter settings have varied among studies ranging from 0.01 to 0.1 Hz,[15] and the degree of infraslow activity in other frequency bands remains unknown.

The definition of infraslow activity has also been variable. Aladjalova first recorded rhythms with frequencies of 0.01-0.1Hz from the neocortex of rabbits in 1957.[16] Vanhatalo et al. defined a frequency range between 0.0 Hz and 0.2 Hz as infraslow

oscillations (ISOs).[14,17] Thordstein et al.[18] showed 0.05- to 70-Hz activity in post-asphyctic full-term neonates, and termed 0- to 1-Hz activity as very low-frequency activity (VLFA).[18] Rodin et al. and other researchers have used 0.01-0.1 Hz and 0.01-0.5 Hz,[19-22] but reported 0.1- to 0.9-Hz activities as cerebral electromagnetic activity in the subdelta range.[23] The definition of 0.01-0.1 Hz has seen frequent use in recent years.[15,24-26] However, some studies have used other definitions, such as 0.07-100 Hz.[27] In short, infraslow activity was defined recently as rhythms with frequencies of 0.01-0.1 Hz. The present study focused on rhythms with frequencies >0.08 Hz (time constant, 2 s), since such activity is easily confirmed in clinical situations. However, the frequency band of the activity is larger than the recently reported values for infraslow activity[15,24-26] We therefore use the term “short infraslow activity (SISA)” for activity between 0.08 and 0.5 Hz in this article, to distinguish such activity from “infraslow activity”.

The aim of the present work was to investigate whether SISA was observed in acute anoxic encephalopathy. If present, we aimed to investigate the relationship between this activity and clinical profiles such as prognosis and acute symptomatic seizures.

2. METHODS

2.1. Patients

Patient characteristics are presented in Table 1. We retrospectively analyzed records of EEG for 98 consecutive acute comatose patients (71 males, 27 females; mean (± standard deviation) age, 65.7 ± 15.4 years) from acute anoxic encephalopathy. All EEGs were recorded in an intensive care unit after successful resuscitation from cardiac arrest. Two patients (one <18 years old, one with acute stroke) were excluded. Among the 98 records of EEG, 40 were recorded at Kyoto University Hospital between April 2008 and September 2015, and 58 were recorded at Kobe City Medical Center General Hospital between January 2012 and September 2015.

Thirty-six patients (36.7%) experienced in-hospital cardiac arrest. Acute post-hypoxic myoclonus[28] and acute symptomatic seizures occurred in 42 patients (42.8%). Among 42 patients with acute post-hypoxic myoclonus or acute symptomatic seizures, 37 patients showed acute post-hypoxic myoclonus alone, 2 patients had generalized tonic-clonic seizures alone, and 3 patients had both. As for treatment, all patients were treated according to the standard protocols for acute anoxic encephalopathy. In addition,

29 patients (29.6%) received mild therapeutic hypothermia in the first 24 h, reducing the body temperature to 34°C with a cooling pad and then rewarming to normothermia. Propofol and fentanyl were also used for sedation and to prevent shivering until body temperature had reached normothermia. The primary outcome measure was neurological outcome, expressed as the score for the Cerebral Performance Category (CPC)[29,30] after 3 months. Good neurological outcome was defined as a CPC score of 1 or 2 (no or moderate disability, respectively), and poor neurological outcome was defined as a score of 3, 4, or 5 (severely disabled, comatose, or deceased, respectively). In the present study, only 6 patients (6.1%) achieved good outcomes (CPC score of 1 or 2) among the 98 patients (Table 1).

2.2 Recordings from EEG

Scalp-recorded EEG was obtained in the conventional manner with a multichannel EEG machine (Nihon Kohden, Tokyo, Japan) using 21 Ag-AgCl electrodes with the International 10-20 system. EEGs were recorded for at least 20 min. The sampling rate was set at 500 Hz and the time constant was 2 s. EEG was recorded

from 4 h to 8 days (mean, 2.4 ± 1.6 days) after resuscitation, and was recorded during mild therapeutic hypothermia in 14 cases. EEGs were recorded at 8 days in three patients, and at 6 days in two patients after cardiopulmonary arrest. The remaining patients (94.9%) underwent EEG recording within 5 days after cardiopulmonary arrest. Artifacts were monitored and electromyographic artifacts were eliminated by neuromuscular blockade in some patients.

2.3. EEG analysis

For this study, each EEG was visually analyzed in the conventional manner by two certified electroencephalographers blinded to clinical data. EEGs were analyzed with a sensitivity of 2-10 μV/mm. One record of EEG was excluded from analysis due to abundant artifacts on EEG. We therefore employed 97 records of EEG from 98 patients.

First, we conventionally classified EEG patterns into 9 categories (electrocerebral inactivity, background suppression, burst suppression, periodic discharge, delta coma, alpha coma, diffuse slowing, spindle coma and normal).

Electrocerebral inactivity, background suppression, burst suppression and periodic discharge were supposed to be associated with poor prognosis according to previous studies.[2,31,32] In addition, burst-suppression pattern was divided into two subtypes depending on whether the identical bursts occurred. "Burst-suppression with identical bursts" was considered present if the shapes of the bursts in the first 500 ms were identical;[33] otherwise, we considered the pattern as "Burst-suppression without identical bursts".

Second, SISA was displayed and evaluated in a referential or average montage using a time constant of 2 s and a high-cut filter of 120 Hz. SISA was defined as sustained negative and/or positive potentials lasting >3 s, as in the previously described method with the following modification for practical usage in clinical situations[10,12]: peak-to-peak amplitude >10 μV in a 1-min epoch as an operational definition in this study. We checked the reproducibility of SISA with regard to location, waveform, duration, and amplitude within each patient. We carefully distinguished artifacts of slower frequency such as respiratory or body movements by visual analysis of simultaneous video, EEG and electromyogram (EMG) recordings and time-frequency analysis of EEG. The fast Fourier

transform (FFT) module was applied for time-frequency analysis in order to evaluate EMG artifacts, which suggest body movements.

We also calculated mean and standard deviation of parameters of SISA: interval, duration, frequency of burst phase coinciding with SISA and amplitude within each patient. The definition of parameters of SISA (namely the onset, end, duration and amplitude) were almost the same as in our previous work.[12] The onset of SISA was defined as the onset of the beginning of the earliest negative slow shift. The end of SISA was defined as the inflection point at the end of the negative slow shift. The duration was defined as the interval between the onset and end. The amplitude was defined as the absolute maximum difference between onset and the next peak of the shift, usually with the largest excursion from onset. We measured the duration and amplitude of SISA using software produced by Nihon Kohden.

The ethics committee of the two hospitals approved the entire protocol as a retrospective study.

2.4. Statistical analysis

We analyzed: 1) the occurrence rate of acute post-hypoxic myoclonus or acute symptomatic seizures; and 2) the rate of good outcomes (CPC score 1 or 2) in both patients with SISA and patients without SISA. For statistical analysis, we used Fisher's extact test. Values of $P < 0.05$ were considered statistically significant.

3. RESULTS

3.1. Findings from conventional EEG

EEG findings are summarized in Table 2. All patients showed abnormalities on EEG. Findings suggestive of poor prognosis (electrocerebral inactivity, background suppression, burst suppression and periodic discharge) were identified in 48 patients (49.0%).

3.2. SISA

We found SISA in only 6 of 97 patients (6.2%). All these instances represented generalized activity and occurred during the burst period of burst-suppression. In this study, all patients with burst suppression displayed SISA. No patients with electrocerebral

inactivity showed SISA. The duration of negative SISA (negative duration) ranged from 3 to 10 s (Figure 1A, B). Three patients showed a burst-suppression pattern with identical burst (Table 3). The intervals of infraslow activities varied among patients, ranging from 5 s to 50 s (Table 4). Although the so-called "burst" period with SISA mainly involved theta (4-7 Hz) and alpha (8-13 Hz) activity, delta-range activity (3-4 Hz) was also seen (Table 4). Time-frequency analysis of EEG revealed that the frequency of fast activity on SISA was <50 Hz and also revealed no electromyographic artifacts (Figure 1C).

All 6 patients with SISA showed acute post-hypoxic myoclonus or acute symptomatic seizures (Table 3). Five patients showed acute post-hypoxic myoclonus of the whole body, 1 patient experienced generalized tonic-clonic seizures and 1 patient had both. Three patients died during hospitalization and no neurological improvements (CPC score 4) were seen in the remaining 3 patients (Table 3). The occurrence rate of acute post-hypoxic myoclonus and acute symptomatic seizures in patients with SISA (100%) was significantly higher than in patients without SISA (39.1%) (Fisher's exact test, $P = 0.0067$, sensitivity = 13.6%, specificity = 100%) (Table 5), although the prognosis did not differ significantly between patients with SISA and those without SISA (Fisher's exact

test, P = 0.68, sensitivity = 6.5%, specificity = 100%) (Table 5).

4. DISCUSSION

The present study found that SISA with a negative duration of 3-10 s occurred infrequently during acute anoxic encephalopathy (6.2%). All SISA coincided with a burst phase of burst-suppression. All patients with SISA also produced acute post-hypoxic myoclonus and acute symptomatic seizures.

4.1. Association with prognosis, acute post-hypoxic myoclonus and acute symptomatic seizure

To the best of our knowledge, only two studies have reported infraslow activity in acute coma patients, and one study examined infraslow activity in adult patients with acute anoxic encephalopathy.[15,18] One of those studies showed infraslow activity in all 41 patients with acute anoxic encephalopathy, but the frequency of activity was 0.015-0.06 Hz with the band-pass filter set at 0.01-0.1 Hz and continuous EEG recording for 2-3 days after admission.[15] Frequency bands and occurrence rates thus differed from those in our

study. Another study examined SISA in acute hypoxic and ischemic encephalopathy of neonates.[18] In that study, the duration of negative SISA was around 4 s, resembling that of our study, but the polarity derivation was opposite in the anterior and posterior directions of the head.

As for the prognosis of patients, those two previous studies reached opposing conclusions. In one study, overall outcomes were poor when the maximum amplitude of infraslow activity was >35 μV.[15] Conversely, high-amplitude SISA (>20 μV) was associated with favorable outcomes in the other study.[18] In the present study, patients with SISA showed poor outcomes, but the number of those patients was small, and prognosis was also poor in patients without SISA. This may suggest that the presence of SISA during burst phase is more specific for poor prognosis, and thus absence of SISA may suggest good prognosis. Nevertheless, we should remain rather cautious of prematurely reaching for conclusions regarding the association between SISA and prognosis.

In our patients, the occurrence rate of acute post-hypoxic myoclonus and acute symptomatic seizures were significantly higher in patients with SISA than in patients without SISA. Although the exact pathophysiology that leads to acute post-hypoxic

myoclonus is unclear and the myoclonus could potentially arise from a subcortical structure such as the brainstem,[28,34] the myoclonus can also be associated with seizures.[35,36] We therefore evaluated acute post-hypoxic myoclonus in addition to acute symptomatic seizures such as generalized tonic-clonic seizures.

Since SISA always occurred with burst-suppression in one-to-one correspondence in the present study, burst-suppression itself may be associated with or share the pathophysiology of acute symptomatic seizures, and less information may be contained in the findings of SISA. However, whether burst-suppression has an epileptic nature remains unclear, because volatile anesthetics induce burst-suppression after counteracting status epilepticus.[37] Taken together, at least the combination of burst-suppression and SISA is associated with acute post-hypoxic myoclonus or acute symptomatic seizures, particularly in critically ill patients with acute anoxic encephalopathy. Although the exact reason for SISA coinciding with burst-suppression was unclear from the present results, a previous study showed that infraslow activity (<0.1 Hz) modulates cortical excitability.[15] We hypothesize that SISA may play a similar role.

In the present study, timing of EEG was different in each patient and thus could have affected conventional EEG findings. EEGs from three patients were recorded at 8 days and those of two patients were recorded at 6 days after cardiopulmonary arrest. EEG findings in these patients were background suppression, generalized periodic discharge and diffuse slowing in 3 patients, but none showed SISA. The remaining patients (94.9%) underwent recording within 5 days from cardiopulmonary arrest. As for findings of SISA, we concluded that the timing of EEG record did not affect our results.

4.2. Generator mechanism for SISA

Localized SISA recorded during epileptic seizures represented localized activity of glial function, whereas activity in the present study was generalized.[10,12] Thus, some differences in generator mechanisms exist between these types of activity. The generator mechanism of SISA in anoxic patients remains unclear, but the activity involves inputs from the subcortical structures[14] in addition to non-neuronal sources such as glia.[38] In the thalamic relay nuclei, some cells have infraslow oscillations[39] and may represent

generator mechanisms of SISA, as seen in the present study.

The onset time of SISA was also important for considering the generator mechanism. As shown in Table 3, EEGs were recorded in 5 of 6 patients presenting with SISA within 1 day, while EEG in the remaining patient was recorded 3 days after cardiopulmonary arrest. If SISA was seen only early in the post-anoxia period, medication, duration of anoxia, use of hypothermia, and co-existence of other disorders could be contributing factors. SISA occurring in the late phase of the post-anoxia period may reflect glial participation, but medication, seizure control and so forth could also be contributing factors.

4.3. Clinical Utility

Previous studies of infraslow activity or ictal slow shifts were recorded with a time constant of 10 s[10-12] or with a very low frequency setting for band-pass filtering.[15,24-26] However, the present study successfully recorded SISA with a time constant of 2 s as a clinically approved amplifier. If the duration or amplitude of infraslow activities is sufficiently high, activity can be recorded with a time constant of 2 s as a commonly used,

clinically approved amplifier.

4.4. Limitations

Several limitations must be considered in this study. First, the number of patients with SISA was relatively small, impeding clarification of the relationship between SISA and prognosis. If patients without SISA during burst suppression had been present, we could have evaluated the significance of SISA for defining prognosis. However, the results may suggest that the presence of SISA during the burst phase shows high specificity (100%) for poor prognosis despite the small number of patients presenting SISA. The absence of SISA during burst suppression may also suggest good prognosis. The present study was retrospective and this fact also limits the ability to reach conclusions regarding the clinical significance of SISA. Prospective studies are needed as a step toward confirming the clinical meanings of SISA.

Second, our recordings from EEG were not continuous and the interval between EEG and cardiac arrest varied over the time course. We may have experienced sampling errors for SISA that would occur during continuous EEG recordings, because SISA was

often periodic.[15] That may be one reason explaining our low occurrence rate.

Third, effects of treatments (propofol, midazolam and mild therapeutic hypothermia) may need to be considered. Although propofol could modulate EEG, propofol-induced EEG changes include increased amplitude of background activity, anteriorization of the alpha rhythm,[40] and induction of burst-suppression. Burst-suppression induced by propofol is morphologically heterogeneous.[41] In the present study, among patients with burst-suppression, the only patient receiving propofol (Patient 2) showed identical burst-suppression. In addition, in a previous study, propofol-induced burst-suppression needed high-dose infusion (14-30 mg/kg/h),[41] whereas the dose of propofol used for Patient 2 was relatively low (1 mg/kg/h). Midazolam also induces burst-suppression and is often used for the treatment of refractory status epilepticus, but also needs high-dose infusion (0.19-0.22 mg/kg/h) for these effects.[42,43] Our Patients 1 and 6 received relatively smaller doses of midazolam (0.03-0.04 mg/kg/h). Two of our six patients (Patients 5 and 6) with SISA were receiving mild therapeutic hypothermia. The target temperature in the present study was 34 °C, and achieving hypothermia to a level of 33-34 °C produces only marginal

alterations in EEG without changes in amplitude.[44] Deep hypothermia for surgery requiring total circulatory arrest aims at achieving a rectal temperature <20 °C.[45] It was reported that only theta and beta activity increased and alpha activity decreased,[44] but no reports appear to have described intermittent activity similar to SISA during mild hypothermia. As for slow waves during infusion of propofol and midazolam, delta oscillations <4 Hz sometimes occur with alpha or beta oscillations,[46,47] but no obvious intermittent activity similar to SISA has been described. Although high-dose infusion of propofol and midazolam could induce burst-suppression, less than one-quarter of a high dose was actually administered to our patients. In addition to these lines of evidence, two patients in the present study showed SISA while receiving neither anesthesia nor mild hypothermia. Taken together, propofol, midazolam and mild therapeutic hypothermia thus seem less likely to have modified burst-suppression or SISA, although other conventional EEG findings could have been affected. However, we cannot completely assert that SISA has no association with drug effects, since SISA was not reported in other situations.

5. Conclusions

In conclusion, SISA was identified in acute anoxic encephalopathy, although the occurrence rate was low. Activity in the present study probably differs at least slightly from the infraslow activity reported in previous studies in terms of frequency and occurrence rate of activity. The differences in frequency and occurrence rate of activity in the present study may be attributed to differences in methods of recording, particularly filter settings.

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Author contributions

MT contributed to initiation and planning of the project, aided in the chart review and data collection, wrote the first draft of the manuscript, edited subsequent drafts and created tables and figures. TH aided in the analysis of data from EEG and edited manuscripts. TM aided in data analysis. MM contributed to the production of scripts for analyzing data from EEG. RM contributed to conception, design, analysis and interpretation. HY, MK, NK provided additional patient information and aided in data collection. RT contributed to conception and design. AI contributed to the initiation and conceptualization of the project, performed analysis of data from EEG, and edited the manuscript.

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Figure legends

Figure 1. Representative waveforms in referential montage and time-frequency analysis of SISA in Patient 2.

A) Activity with time constant of 0.1 s. B) Activity with time constant of 2 s. C) Time-frequency analysis and waveforms of SISA.

SISA is more clearly delineated with a time constant of 2 s (B, black line) than with a

time constant of 0.1 s. Time-frequency analysis (0-100Hz) showed increased power of low-frequency band and no electromyographic artifact. SISA was evaluated in a monopolar montage F3-A1 and F4-A2 with high-cut filter 1Hz and low-cut filter 0.08Hz.

Figure 1

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Figure 1.

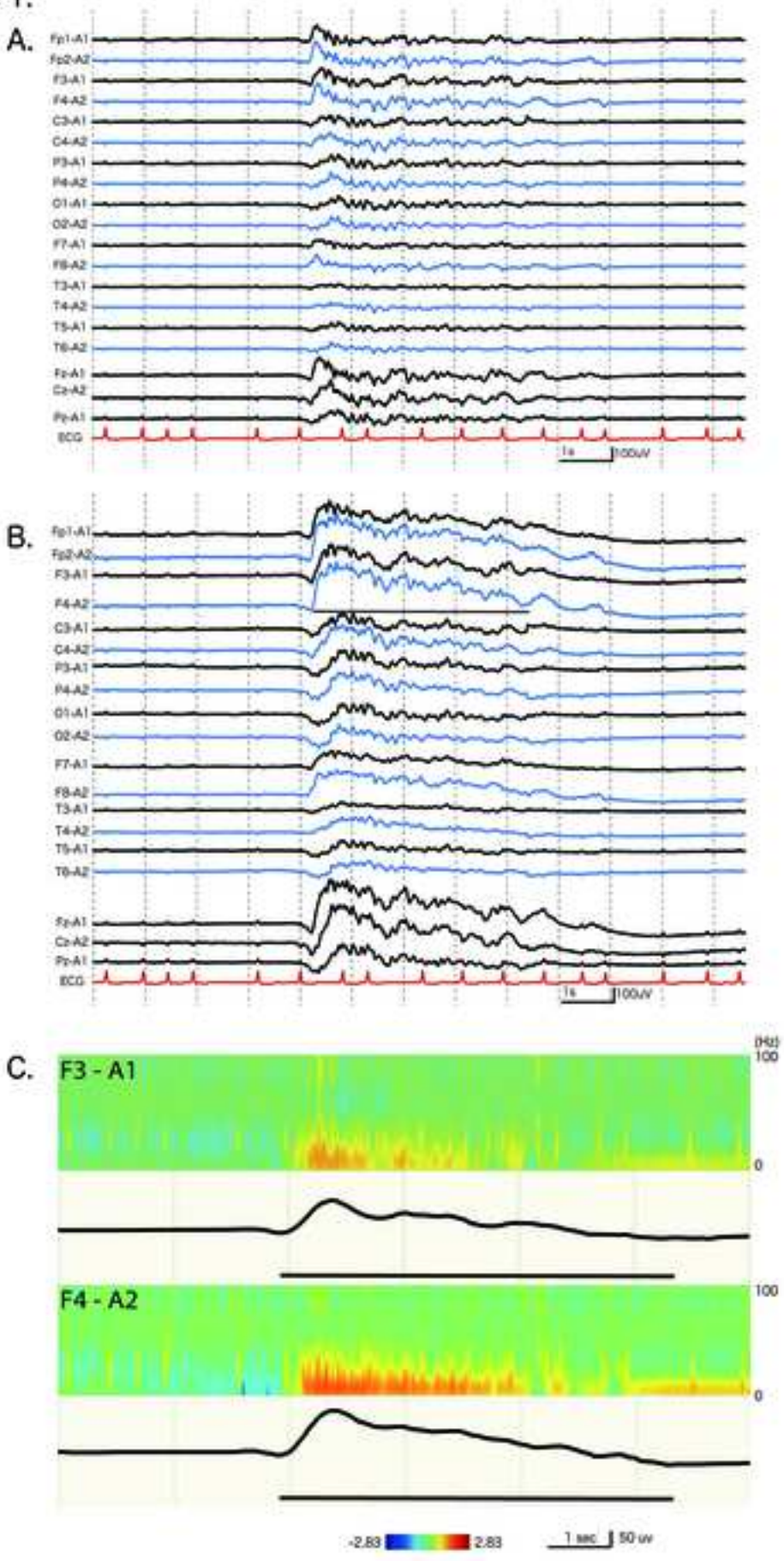

Figure 1.

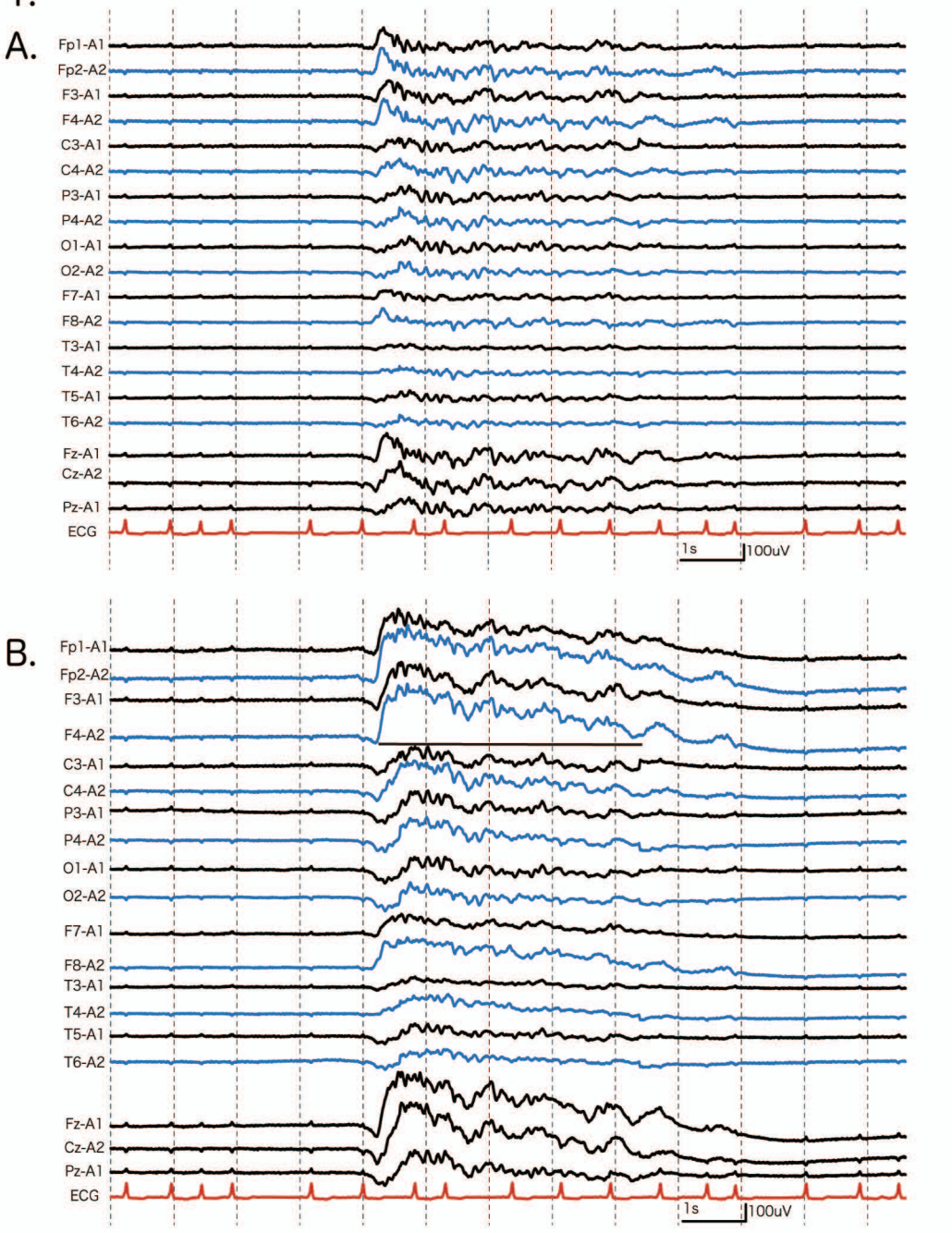
A.
Fp1-A1
Fp2-A2
F3-A1
F4-A2
C3-A1
C4-A2
P3-A1
P4-A2
O1-A1
O2-A2
F7-A1
F8-A2
T3-A1
T4-A2
T5-A1
T6-A2
Fz-A1
Cz-A2
Pz-A1
ECG
1s
100uV
B.
Fp1-A1
Fp2-A2
F3-A1
F4-A2
C3-A1
C4-A2
P3-A1
P4-A2
O1-A1
O2-A2
F7-A1
F8-A2
T3-A1
T4-A2
T5-A1
T6-A2
Fz-A1
Cz-A2
Pz-A1
ECG
1s
100uV
C.
F3 - A1
(Hz)
100
0
F4 - A2
100
0
-2.83
2.83
1 sec
50 uv

Table 1. Patient characteristics

Patients, n	98
Men, n	71 (72.4%)
Age, y	65.7 ± 15.4
Initial cardiac rhythm	
Pulseless electrical activity	29 (29.6%)
Asystole	32 (32.6%)
VF	17 (17.3%)
Time difference from cardiac arrest to resuscitation, min	22.3 ± 18.3
Inhospital	36 (36.7%)
No abnormality in brain CT/MRI	42 (42.9%)
Acute symptomatic seizure	42 (42.9%)
Myoclonic	37 (37.8%)
Generalized tonic clonic	2 (2.0%)
Both	3 (3.1%)
Sedation	
Propofol	26 (26.5%)
Midazolam	16 (16.3%)
Fentanyl	15 (15.3%)
Hypothermia, n	29 (29.6%)
Neurological outcome	
Good (CPC 1-2)	6 (6.1%)
Poor (CPC 3-4)	38 (38.8%)
Death (CPC 5)	54 (55.1%)
EEG recording, day	2.4 ± 1.6 (from cardiac arrest)

CPC: Cerebral Performance Category

1: no disability, 2: moderate disability, 3: severely disabled, 4: comatose, 5: deceased

Table 2. EEG findings

EEG findings	Patient number (n = 98)	Prognosis (mild - severe - deceased)
Electrocerebral inactivity*	5	0 -1 - 4
Background suppression*	22	1 - 11 - 10
Burst-suppression*	6	0 - 3 - 3
Periodic discharge*	15	0 -8 - 7
Delta coma	12	1 - 3 - 8
Alpha coma	2	2 - 0 - 0
Diffuse slowing	34	1 -17 -16
Spindle coma	1	1 - 0 - 0
Inconclusive (due to artifact)	1	1

* EEG findings suggestive of poor prognosis

Table 3. Characteristics of patients with SISA

Patient No./ Sex/Age	CPA time (min)	Onset	Initial Rhythm	Sedation	Mild Hypothermia	Neuroimaging	EEG Recordings (day)	Acute post-Hypoxic Myoclonus/ Acute Symptomatic Seizure	Prognosis	Identical Burst
1/M/61	20	Out of hospital	Asystole	Midazolam (0.04mg /kg/hr)		Basal ganglia Obscure	1	Myoclonus	Death (day 12)	Not Identical
2/F/83	12	Inhospital	Asystole	Propofol (1mg /kg/hr)		Basal ganglia Obscure	0.4	Myoclonus + GTCS	CPC 5	Identical
3/M/85	20	Out of hospital	Asystole	None		Normal	1	Myoclonus	Death (day 8)	Not Identical
4/F/62	30	Inhospital	Asystole	None		Normal	1	Myoclonus	Death (day 2)	Identical
5/M/37	23	Out of hospital	Unknown	None	✓	Diffuse Ischemia	1	GTCS	CPC 5	Not Identical
6/F/53	Unknown	Out of hospital	Unknown	Midazolam (0.03mg /kg/hr)	✓	Normal	3	Myoclonus	CPC 5	Identical

Table 4. Characteristics of SISA (means ± SD)

Patient No./ Sex/Age	Interval (s)	Duration (s)	Burst phase (Hz)	Amplitude (μV)
1/M/61	44.1 ± 10.0	6.0 ± 1.3	4.8 ± 0.5	174.9 ± 49.0
2/M/85	8.7 ± 0.5	5.1 ± 1.9	5.1 ± 1.9	74.3 ± 20.9
3/F/83	17.7 ± 4.9	6.3 ± 0.4	7.1 ± 1.1	334.8 ± 150.0
4/F/62	19.3 ± 5.6	5.4 ± 0.2	5.3 ± 0.2	160.7 ± 8.5
5/M/37	16.6± 5.4	4.2 ± 1.3	5.5 ± 2.0	41.3 ± 6.7
6/F/53	7.7 ± 2.5	5.2 ± 1.4	8.7 ± 2.4	361.8 ± 37.1

Table 5. Occurrence rate of acute post-hypoxic myoclonus or acute symptomatic seizure and rate of poor outcome

	Myoclous or Seizure +	Myoclonus or Seizure -
SISA +	6	0
SISA -	38	54

P = 0.0067 (Fisher exact test)

Sensitivity = 13.6%, Specificity = 100%

	Poor prognosis	Good prognosis
SISA +	6	0
SISA -	86	6

P > 0.05 (Fisher exact test)

Sensitivity = 6.5%, Specificity = 100%