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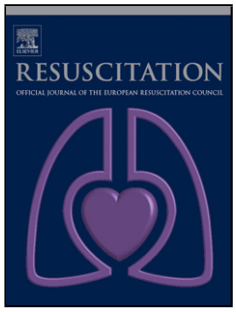
Peer-reviewed author version

Haesen, Jolien; EERTMANS, Ward; GENBRUGGE, Cornelia; MEEX, Ingrid; Demeestere, Jelle; VANDER LAENEN, Margot; BOER, Willem; MESOTTEN, Dieter; DENS, Jo; JANS, Frank; Ernon, Ludovic & DE DEYNE, Cathy (2018) The validation of simplified EEG derived from the bispectral index monitor in post-cardiac arrest patients.. In: RESUSCITATION, 126, p. 179-184.

DOI: 10.1016/j.resuscitation.2018.01.042
Handle: http://hdl.handle.net/1942/25876



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PII: S0300-9572(18)30052-2
DOI: https://doi.org/10.1016/j.resuscitation.2018.01.042
Reference: RESUS 7473

To appear in: *Resuscitation*

Received date: 28-10-2017
Revised date: 11-1-2018
Accepted date: 27-1-2018

Please cite this article as: Haesen Jolien, Eertmans Ward, Genbrugge Cornelia, Meex Ingrid, Demeestere Jelle, Laenen Margot Vander, Boer Willem, Mesotten Dieter, Dens Jo, Jans Frank, Ernon Ludovic, De Deyne Cathy.The validation of simplified EEG derived from the bispectral index monitor in post-cardiac arrest patients.*Resuscitation* https://doi.org/10.1016/j.resuscitation.2018.01.042

The validation of simplified EEG derived from the bispectral index monitor in post-cardiac arrest patients

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Total word count

Paper = 2936 words

Abstract = 250 words

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Abstract

Aims

We aimed to validate retrospectively the accuracy of simplified electroencephalography (EEG) monitoring derived from the bispectral index (BIS) monitor in post-cardiac arrest (CA) patients.

Methods

Successfully resuscitated CA patients were transferred to the Catherization Lab followed by percutaneous coronary intervention when indicated. On arrival at the coronary care unit, bilateral BIS monitoring was started and continued up to 72 hours. Raw simplified EEG tracings were extracted from the BIS monitor at a time point coinciding with the registration of standard EEG monitoring. BIS EEG tracings were reviewed by two neurophysiologists, who were asked to indicate the presence of following patterns: diffuse slowing rhythm, burst suppression pattern, cerebral inactivity, periodic epileptiform discharges and status epilepticus (SE). Additionally, these simplified BIS EEG tracings were analysed by two inexperienced investigators, who were asked to indicate the presence of SE only.

Results

Thirty-two simplified BIS EEG samples were analysed. Compared to standard EEG, neurophysiologists interpreted all simplified EEG samples with a sensitivity of 86%, a specificity of 100% and an interobserver variability of 0.843. Furthermore, SE was identified with a sensitivity of 80% and a specificity of 94% by two unexperienced physicians.

Conclusion

Using a simple classification system, raw simplified EEG derived from a BIS monitoring device is comparable to standard EEG monitoring. Moreover, investigators without EEG experience were capable to identify SE in post-CA patients. Future studies will be warranted to confirm our results and to determine the added value of using simplified BIS EEG in terms of prognostic and therapeutic implications.

Key words

Bispectral index – simplified electroencephalography – neuromonitoring – cardiac arrest – status epilepticus

Introduction

Up to one third of the cardiac arrest (CA) survivors develop seizures which often remain underdiagnosed as most of them are classified as non-convulsive ones.[1, 2] Multiple studies already showed that the development of seizures is associated with a poor prognosis.[3, 4] Moreover, early detection of these seizures is of the utmost importance since mortality increases exponentially with their duration.[2, 5, 6] Unfortunately, there is still a delay in the identification of these harmful seizures in most post-CA patients as full or continuous EEG (cEEG) recording is rarely performed in the early hours following CA.[7, 8] This emphasizes the need for a simple but accurate EEG tool to identify aggravating neurological conditions and secondary cerebral insults such as epileptic activity. Patients who experience epileptic seizures might benefit the most from a specific treatment in case of early detection.[9-12]

The bispectral index (BIS) monitor is an easy to use and rapidly deployable 4-channel quantitative EEG system.[13] Although the BIS monitor, with incorporated BIS value calculation (0 – 100), is developed to measure the depth of consciousness during general anaesthesia, several studies have used the BIS value to guide neurological prognostication after CA.[14, 15] The overall goal of this study, however, was to validate retrospectively simplified raw EEG tracings derived from the BIS monitor against standard EEG monitoring in order to identify seizures and other ominous patterns often observed in post-CA patients.

Methods

From March 2011 to April 2014, all adult comatose patients successfully resuscitated CA patients were admitted to the coronary care unit (CCU) in Ziekenhuis Oost-Limburg (Genk, Belgium). This retrospective study, based on prospectively gathered BIS data, aimed to validate the accuracy of simplified EEG obtained from the BIS monitor (BIS EEG) against full intermittent EEG. Therefore, only patients in whom the BIS monitor was still applied at the moment a full intermittent EEG was performed, were retrospectively selected for enrolment in this validation study. Approval of the local ethical committee was obtained before the onset of the study (CME11/066) and written informed consent was obtained from the patient's next of kin and was reconfirmed if patients regained consciousness.

Patient management

According to the institutional protocol, targeted temperature management (TTM) at 33°C was immediately started after admission to the emergency department and was further maintained at the CCU for 24 hours after which patients were gradually rewarmed at a rate of 0.3°C/h over the following 12 hours.[16, 17] Sedation was maintained by intravenous administration of propofol, midazolam and remifentanil. In line with current guidelines, patients received cisatracurium only in case of shivering. All patients were intubated and mechanically ventilated. At the end of rewarming, sedation was reduced to facilitate assessment of patients' neurological status. Patients unready for extubation due to respiratory, circulatory complications or due to persisting coma remained sedated with the lowest dose necessary to tolerate endotracheal intubation. Full standard EEG registrations were performed routinely after the return to normothermia (i.e. at about 36 hours after CA) or in case of a clinical indication. These EEG measurements were digitally recorded with a 19-channel system, arranged according to the international 10-20 system. Every EEG was characterized by a description of the posterior dominant rhythm (or absence thereof) and amplitude as well as the presence of non-dominant rhythms. Lateralization and the presence of artefacts was described where applicable. If present, epileptic activity was described as interictal, ictal or as status

epilepticus. Patients with epileptic activity, based on standard EEG measurements, were treated with antiepileptic drugs, often in combination with midazolam and propofol. Although treating physicians were not blinded, BIS values were not used for titrating depth of sedation. Furthermore, withdrawal of life support was not based on the simplified EEG measurements displayed on the BIS monitor, but was in line with international guidelines and relied on a clinical evaluation, full EEG measurements and somatosensory evoked potentials (SSEP) instead.[18]

Bispectral index monitoring

On arrival at the CCU, bilateral BIS monitoring using the BIS VISTA™ (Aspect Medical Systems, Inc. Norwood, USA) was started as soon as possible and continued up to 72 hours. The BIS monitor provides a real-time number using an easily applicable six-electrode forehead sensor (BIS™ bilateral sensor), which was applied to the frontotemporal area before the start of TTM. Aside from the BIS value itself, the BIS VISTA™ monitor also displays bilateral frontotemporal EEG traces (Fig. 1). To compare these simplified EEG traces derived from the BIS monitor with standard intermittent EEG, raw BIS EEG traces of at least five consecutive minutes were retrospectively extracted at a time point that coincided with the registration of a standard full EEG using the DATALOGGER Data Review Program for Windows (Aspect Medical Systems inc.;version 0.04.07;1995). Afterwards, these small BIS EEG frames were reviewed by two experienced neurophysiologists (LE and JD) who were blinded to patients' clinical course and neurological outcome. They were asked to indicate the presence of five simple EEG patterns (i.e. diffuse slowing rhythm, burst suppression pattern, cerebral inactivity, epileptic activity/PEDs or status epilepticus (SE)) based on the classification system used by Rundgren et al..[19, 20] After calculating the inter-observer variability, a consensus decision was made by the two neurophysiologists in case of any discrepancies.

In order to further validate the ease of use of the simplified BIS EEG by unexperienced physicians, two investigators (IM and CG) without any experience in the interpretation of EEG, analysed the same simplified BIS EEG frames as were given to the neurophysiologists. They were specifically asked to focus only on the detection of epileptiform activity. Figure 2 was used as an

example of typical EEG tracings after CA in order to instruct the non-qualified investigators.

Data collection

Baseline demographics including gender, age and information regarding drug administration were extracted from the electronic medical record. Cardiopulmonary resuscitation (CPR) details such as initial rhythm and bystander CPR were extracted from the Utstein data. Time to return to spontaneous circulation (ROSC) was determined as time of collapse to time of ROSC. Patients' outcome was graded according to the Cerebral Performance Category (CPC) score at 6 months.[21] CPC-scores were dichotomized as good (CPC 1-2) or poor neurological outcome (CPC 3-5).

Statistical analysis

All analyses were conducted using SPSS Version 24.0 (IBM Corp., Armonk, NY, USA). Continuous data were presented as mean with standard deviation and categorical variables as counts and percentages (%). Equal distribution was tested using a Shapiro-Wilk test. Depending on normality, categorical date were analysed using a Fisher exact or a Pearson Chi-Square test, while an unpaired T-test or Mann-Whitney U test was used for continuous data. Correlations were calculated using Pearson's or Spearman's coefficient of correlation, depending on normality. Sensitivity and specificity were calculated for the correct detection of the aforementioned five EEG patterns. A p-value<0.05 was considered significant.

Results

Patient characteristics

Between 2011 and 2014, 115 comatose CA survivors were enrolled in this study and BIS monitoring was started in 88 patients treated with TTM at 33°C (Fig. 3). Thirteen subjects were excluded due to invalid data caused by technical difficulties (n = 12) and hemodynamic instability resulting in death within the initial hours following admission (n = 1). In 32 out of these 75 retained patients, the BIS monitor was still applied at a time point coinciding with the performance of a full standard EEG. At 180 days post-CA, 14 out of these 32 patients (44%) had a good neurological outcome (CPC1-2), while 18 patients (56%) had a CPC of 5. There were no patients with a CPC of 3 or 4 at 180 days post-CA. Baseline characteristics of both outcome groups are summarized in table 1. Interestingly, all patients who experienced a SE had a poor neurological outcome ($p<0.001$).

Validation

In total, 32 simplified BIS EEG samples were analysed at a time point coincident with the registration of full standard EEG monitoring, in order to compare the concordance of both EEG options. The time of validation was at day 3±1 after CA and was not different between patients with a good and poor neurological outcome ($p=0.613$; Table 1). According to the standard EEG measurements, 11 (34%) recordings showed a diffuse slowing pattern, six (19%) a burst suppression pattern, three (9%) recordings showed cerebral inactivity, four (13%) indicated PEDs and 8 (25%) recordings showed a SE (Table 2). As compared to these standard EEG measurements, neurophysiologist I misinterpreted simplified BIS EEG samples, whereas neurophysiologist II misdiagnosed six of them. As such, neurophysiologist I classified all analysed BIS EEG samples with a sensitivity of 86% and a specificity of 91%, while neurophysiologist II reached a sensitivity and specificity of 71% and 100%, respectively. After consensus was actively asked for, all BIS EEG samples were correctly analysed with a sensitivity of 86% and a specificity of 100% (Table 2).

In fact, only one SE was missed by one neurophysiologist. Most other misdiagnosed recordings showed a pattern of PEDs according to the standard EEG measurements, while the

simplified BIS EEG samples were interpreted as a diffuse slowing pattern. Three of them (75%) were misinterpreted by both neurophysiologists. Therefore, sensitivity for the classification of PEDs based on simplified BIS EEG samples is 25%.

A high level of agreement was observed between the two independent neurophysiologists (kappa = 0.843). There was a strong correlation between full and simplified BIS EEG for both neurophysiologists, with a mean correlation of r = 0.810 ($r_{\text{neurophysiologist I}}$ = 0.852 and $r_{\text{neurophysiologist II}}$ = 0.767).

To test whether physicians without any EEG experience would be able to detect epileptic activity using simplified BIS EEG traces, two independent and unexperienced investigators were asked to indicate the presence of a SE on the same BIS EEG samples as were given to the neurophysiologists. One investigator missed only one patient diagnosed with SE, whereas the other investigator missed three patients. Additionally, three patients without SE on full EEG were falsely indicated as at risk for epileptic activity. As such, one investigator identified patients diagnosed with SE with a sensitivity of 90% and a specificity of 92%, whereas the other one reached a sensitivity of 70% and a specificity of 96%.

Discussion

This was a retrospective validation study showing that: 1) raw simplified EEG traces derived from a BIS monitor correlate well with standard EEG when a simple classification system is being used in a post-CA-setting, and 2) non-experienced investigators are able to detect epileptic activity/SE on the BIS EEG monitor with a high level of accuracy.

To data, it remains to be elucidated whether the treatment of seizures effectively improves neurological outcome, or that seizures are simply a clinical expression of the post-ischemic damage questioning the benefit of any treatment efforts. Nonetheless, guidelines still advocate the use of anti-convulsive therapy in case of seizures, and therefore cEEG monitoring has been recommended in comatose CA patients treated with TTM.[18, 22] Unfortunately, cEEG is expensive and labour-intensive but more importantly, most of the available cEEG devices still require continuous availability of expertise for a correct interpretation. In order to become generally applicable, it should be simple, cost-effective and easy to use at the bedside.[23-25] A simplified EEG monitor would overcome these limitations and would allow us at the same time to detect non-convulsive seizures in an early stage.

Numerous studies have already investigated BIS monitoring to assist in neurological prognostication after CA.[14, 15, 26] Furthermore, it has been suggested that the BIS monitor might be used to detect non-convulsive seizures as their occurrence is accompanied with fluctuations of the BIS value.[27-30] In fact, the BIS monitor samples raw EEG tracings to provide the real-time BIS value. Although these raw EEG tracings are displayed in real-time, the potential to use the BIS device as a simplified EEG monitor after OHCA has not been investigated.

Rundgren et al. already investigated in OHCA patients the prognostic role of amplitude-integrated EEG, another simplified EEG tool, although it was not fully validated against standard EEG.[19, 20] It is for this reason that we preferred to validate first the accuracy of simplified EEG traces obtained by the BIS monitor before providing prognostic values. As such, a similar classification system, as suggested by Rundgren et al., was used consisting out of five simple EEG patterns, i.e. diffuse slowing, burst suppression, cerebral inactivity, PEDs and SE. Using this simple classification

system, this study showed a high concordance between standard and simplified BIS EEG monitoring (r = 0.810). While other studies were able to detect a SE with a sensitivity ranging from 60% to 100%, this study reached an overall sensitivity of 86%, not only for the diagnosis of SE, but for the detection of the entire classification system.[31-34] This strongly indicates that simplified BIS EEG monitoring could be used to detect other ominous EEG patterns aside from a SE as well. In fact, only 9% of all BIS EEG samples were misdiagnosed by both neurophysiologists, all from patients diagnosed with PEDs. It is plausible to assume that these promising results can be partially explained by the combined use of a simplified classification system and simplified EEG monitoring device. Still, early detection of pathologic EEG tracings using a simplified EEG device can only be relevant if it either influences the course of the disease beneficially or if it would assist with the process of neuroprognostication. In this context, our data should be considered as hypothesis-generating since our study results only show that simplified BIS EEG correlate well with standard EEG. Future studies will now be warranted to validate our results and to determine the added value of using simplified BIS EEG in terms of prognostic and therapeutic implications. Unfortunately, our time point of validation was situated approximately three days after CA. As previous studies showed that the prognostic power of EEG lies within the first 24 hours, we acknowledge that the prognostic value of simplified BIS EEG warrants further examination in a similar time window[14, 15, 35-37].

Aside from experienced neurophysiologists, treating physicians should also be capable of interpreting simplified EEG traces on the BIS monitor as they can play a prominent role in the early identification of epileptic activity. This study showed that even unexperienced investigators were able to indicate the presence of a SE with an adequate sensitivity (mean 80%) and specificity (mean 94%). Three patients, however, were identified as at risk for epileptic activity, although no epileptic activity was present on full EEG. Nevertheless, we believe that in case of uncertainty, it is more important to consider treatment for epileptic activity and/or request full EEG measurements as soon as possible rather than delaying until the patient is undoubtedly diagnosed with SE. Although the

benefit of anti-convulsive therapy remains indistinct, this study confirms that electrographic seizures are associated with poor neurological outcome.

In line with our study findings, others already demonstrated the ability of diverse simplified EEG systems with three to seven channels to detect epilepsy accurately.[31, 33] In contrast, Kolls et al. did not confirm the high compliance between a full and simplified hairline EEG system, as only 71% of the samples were correctly interpreted.[32] However, the EEGs samples analysed by Kolls et al. consisted out of very specific EEG patterns (e.g. GPEDs, PLEDs), which are far more difficult to diagnose as compared to the more prominent EEG patterns in post-CA patients. Similarly, we tested the accuracy of our simplified BIS EEG tool to detect PEDs and found that the sensitivity for the detection of these specific patterns was only 25%. This could be explained by the fact that these PEDs as well as other focal epileptic discharges might occur outside the frontotemporal range detected by our simplified BIS EEG device. Therefore, we believe that a simplified EEG monitoring tool should preferably be used to screen for generalized ominous patterns such as cerebral inactivity or SE instead of using it to detect very specific EEG patterns[14, 15, 38]. However, it has to be stated that a full EEG will always be necessary to confirm the diagnosis based on simplified BIS EEG.

Limitations

Several limitations should be acknowledged. First, this validation study was a retrospective analysis which is inherently susceptible to limitations such as selection bias and missing data.. In addition, a single-centre study could have biased the visual analysis of the EEG findings. Therefore, we asked two independent neurophysiologists blinded to each other's results although it has to be stated that a third neurophysiologist to reach consensus would eliminate the risk of a self-fulfilling prophecy. Nevertheless, this validation study should be considered as a hypothesis-generating one which requires confirmation in future multicentre studies with a larger sample size. Secondly, treating physicians were not blinded to the EEG tracings displayed on the BIS monitor as visual confirmation was needed to assure adequate signal quality. Nevertheless, the recorded BIS EEG tracings were not considered for the withdrawal of treatment policy. Finally, the BIS monitor

comprises only the frontotemporal area, which does not provide information about other parts of the brain. Nonetheless, CA generally induces global ischemic brain damage, possibly implying that a frontotemporal sensor might be sufficient to provide valuable electrographic information, especially in the early hours following OHCA where there is often hardly any neuromonitoring present.

Conclusion

This retrospective analysis shows that raw simplified EEG derived from a BIS monitoring device might be comparable to standard EEG monitoring when a simple classification system is being used by experienced neurophysiologists. Furthermore, investigators without any EEG experience were also able to identify epileptic activity in post-CA patients with an adequate accuracy. Nevertheless, multicenter studies are warranted to verify our preliminary study findings and should consider validation sessions at time points where EEG encompasses the highest prognostic power. Additionally, these studies should also determine whether BIS EEG monitoring could influence neurological outcome by detecting epileptic activity in an early phase followed by immediate anti-convulsive therapy.

Conflicts of interests

The authors declare that they have no competing interests.

Acknowledgements

The authors wish to thank the nursing and medical staff of the emergency department, the catheterization lab, the CCU and the department of neurology for their cooperation in this study.

This study was part of the Limburg Clinical Research Program supported by the foundation Limburg Sterk Merk, Hasselt University, Ziekenhuis Oost – Limburg and Jessa Hospital.

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Figure legends

Fig 1. BIS VISTA™ monitor with EEG display. The BIS VISTA™ device is able to display bilateral frontotemporal EEG traces in real-time.

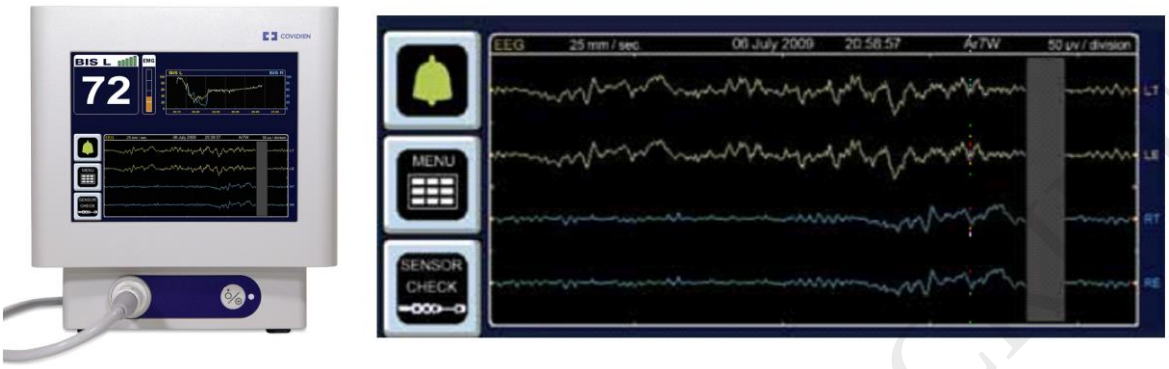


Fig 2. Four typical electro-encephalic patterns after cardiac arrest. These patterns are read-outs from raw simplified frontotemporal EEG traces which can be observed on the BIS monitor.

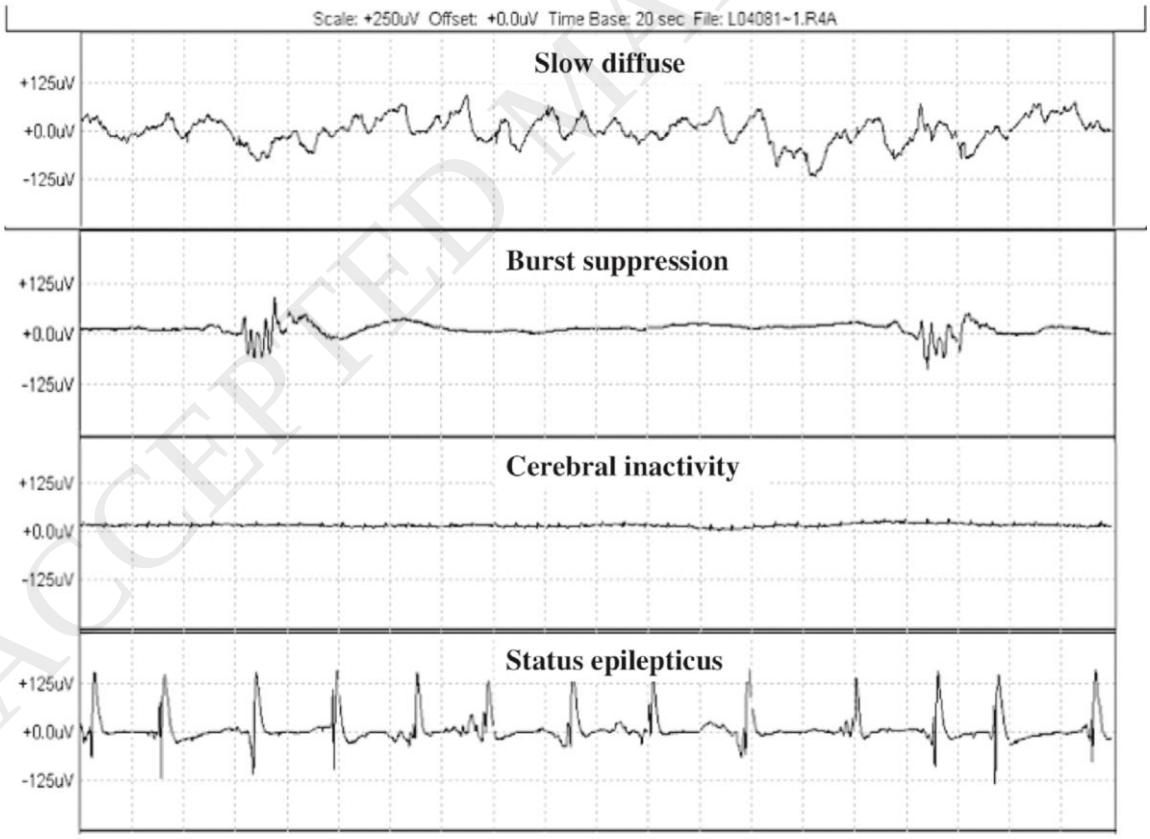
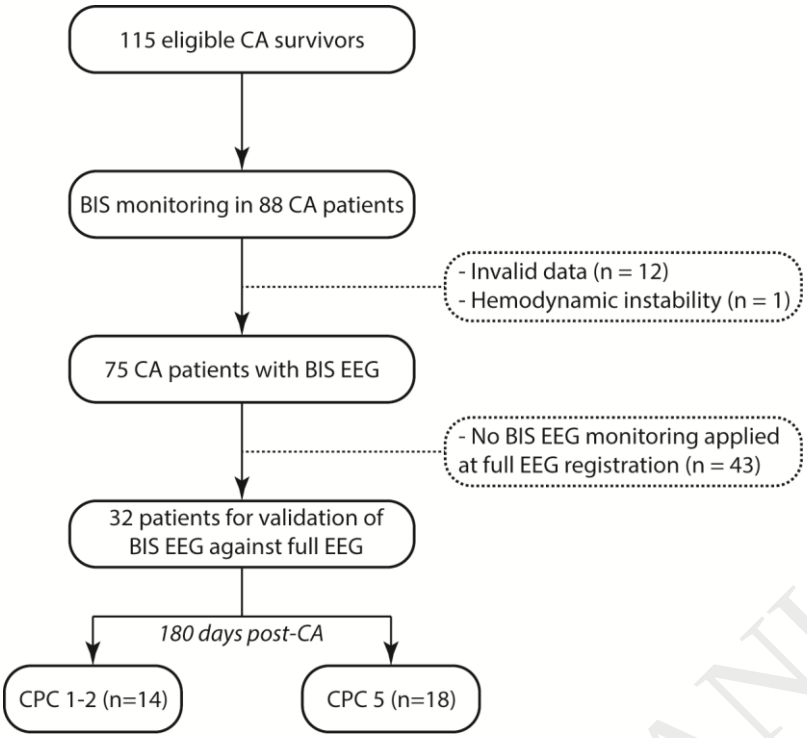


Fig 3. Flowchart of enrolled patients. BIS = Bispectral index; CA = cardiac arrest; CPC = Cerebral Performance Category; EEG = electro-encephalography.



Tables

Table 1. Patient characteristics

	All subjects	Good outcome CPC1-2	Poor outcome CPC3-5	P-value
Subjects, n (%)	32 (100)	14 (44)	18 (56)	
Age	61 ± 14	61 ± 14	61 ± 14	0.796
Male sex, n (%)	23 (72)	10 (71)	13 (72)	0.960
Initial rhythm				
Ventricular arrhythmia, n (%)	24 (75)	12 (86)	12 (67)	0.217
Witnessed arrest, n (%)	27 (84)	13 (93)	14 (78)	0.069
Time to ROSC, minutes	32 ± 20	24 ± 23	39 ± 13	**0.045**
CCU stay, days	10 ± 5	10 ± 5	9 ± 8	0.639
SE, n (%)	12 (38)	0 (0)	12 (67)	**<0.001**
Time of validation, in days after cardiac arrest	3 ± 1	2 ± 1	3 ± 2	0.613
Number of full EEGs	3 ± 1	3 ± 1	3 ± 2	0.866

CPC: cerebral performance score – ROSC: return to spontaneous circulation – CCU: coronary care unit – SE: status epilepticus – EEG: electro-encephalogram.

Table 2. Validation of simplified BIS EEG

EEG patterns	Full EEG	Simplified BIS EEG		
		Neurophys. I	Neurophys. II	Consensus
Slow diffuse (n)	11	10	11	11
Burst suppression (n)	6	6	4	6
Cerebral inactivity (n)	3	3	3	3
PEDs (n)	4	1	1	1
Status epilepticus (n)	8	8	7	8
Total	32	28	26	29
STATISTICS				
Sensitivity (%)		86	71	86
Specificity (%)		91	100	100

EEG: Electroencephalogram – BIS: Bispectral index – PEDs: Periodic epileptic discharges.