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Burst-suppression with identical bursts: A distinct EEG pattern with poor outcome in postanoxic coma

Jeannette Hofmeijer [a,b,*], Marleen C. Tjepkema-Cloostermans [a,c], Michel J.A.M. van Putten [a,c]

[a] Clinical Neurophysiology, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands
[b] Department of Neurology, Rijnstate Hospital, Arnhem, The Netherlands
[c] Department of Clinical Neurophysiology, Medisch Spectrum Twente, The Netherlands

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HIGHLIGHTS

- "Burst-suppression with identical bursts" is a distinct pathological EEG pattern.
- "Burst-suppression with identical bursts" is exclusively observed in patients after diffuse cerebral ischemia.
- "Burst-suppression with identical bursts" is invariably associated with a poor outcome in comatose patients after cardiac arrest.

ABSTRACT

Objective: To assess the incidence, quantified EEG characteristics, and prognostic significance of "burst-suppression with identical bursts" and to discuss potential pathophysiological mechanisms.
Methods: Burst-suppression EEGs were identified from a cohort of 101 comatose patients after cardiac arrest, and from our complete database of 9600 EEGs, since 2005. Patterns with and without identical bursts were classified visually by two observers. Of patients after cardiac arrest, outcomes were assessed at three and six months. Identical and non-identical burst-suppression patterns were compared for quantified EEG characteristics and clinical outcome. Cross correlation of burstshape was applied to the first 500 ms of each burst.
Results: Of 9701 EEGs, 240 showed burst-suppression, 22 with identical bursts. Identical bursts were observed in twenty (20%) of 101 comatose patients after cardiac arrest between a median of 12 and 36 h after the arrest, but not in the six patients with other pathology than cerebral ischemia, or the 183 with anesthesia induced burst suppression. Inter-observer agreement was 0.8 and disagreement always resulted from sampling error. Burst-suppression with identical bursts was always bilateral synchronous, amplitudes were higher (128 vs. 25 μV, $p = 0.0001$) and correlation coefficients of burstshapes were higher (95% >0.75 vs. 0% >0.75, $p < 0.0001$) than in burst-suppression without identical bursts. All twenty patients with identical bursts after cardiac arrest had a poor outcome versus 10 (36%) without identical bursts.
Conclusion: "Burst-suppression with identical bursts" is a distinct pathological EEG pattern, which in this series only occurred after diffuse cerebral ischemia and was invariably associated with poor outcome.
Significance: In comatose patients after cardiac arrest, "burst-suppression with identical bursts" predicts a poor outcome with a high specificity.

1. Introduction

Burst-suppression in the electroencephalogram (EEG) is characterized by high amplitude events (bursts) alternated by periods of low or absent activity (suppressions) (Niedermeijer and Lopes da Silva, 1999; Steriade et al., 1994). This pattern can be physiological, for instance during early development, or pathological, for example in almost half of comatose patients within the first 48 h after

* Corresponding author at: Clinical Neurophysiology, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, The Netherlands. Tel.: +31 88 0058877; fax: +31 88 0058890.
E-mail addresses: jhofmeijer@rijnstate.nl (J. Hofmeijer), M.C.Cloostermans@utwente.nl (M.C. Tjepkema-Cloostermans), M.J.A.M.vanPutten@utwente.nl (M.J.A.M. van Putten).

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cardiac arrest (Cloostermans et al., 2012). Also, burst-suppression can be induced by anesthetics (Yoon et al., 2012). Under pathological conditions, it is usually associated with a poor prognosis. However, in a previous prospective cohort study, we found that 18% of patients with burst-suppression at 12 or 24 h after cardiac arrest had a good functional outcome (Cloostermans et al., 2012).

Characteristics to classify burst-suppression patterns into subgroups with presumed differences in clinical significance include the duration of the bursts and interburst intervals, maximum peak to peak voltage, area under the curve, and the ratio of power in high versus low frequencies (Akrawi et al., 1996). For example, longer suppressions were associated with poorer recovery in patients with postanoxic coma (Wennervirta et al., 2009). Still, predictive values for poor outcome remain too low to allow treatment decisions.

Extreme similarity of burstshape is a distinct feature of some burst-suppression patterns. Herewith, subsequent bursts in a particular channel are almost "photographic" copies. Patterns with this particular characteristic have been sporadically reported and considered a rarity (Hughes, 1986; van Putten and van Putten, 2010). However, through standard use of continuous EEG in comatose patients on the intensive care, we have learned that these occur relatively frequent within the first days after acute diffuse cerebral ischemia.

Here we report on the incidence and prognostic significance of "burst-suppression with identical bursts" and quantify its EEG characteristics. We show that this is a distinct pathological EEG pattern that only occurs after diffuse cerebral ischemia and is invariably associated with a poor outcome in these patients. Since both morphology and clinical significance apparently differ from other burst-suppression patterns, we propose to label the pattern as "burst-suppression with identical bursts." We discuss potential pathophysiological mechanisms.

2. Methods

2.1. Burst-suppression EEGs

We identified EEGs with bursts-suppression in two ways. First, we took these from comatose patients after cardiac arrest that were included in a prospective cohort study on the predictive value of continuous EEG on outcome between June 1st 2010 and September 31st 2012. Design, eligibility criteria, and main outcomes of the first 60 patients included in this study have been published previously (Cloostermans et al., 2012). In brief, since June 1st 2010, consecutive adult comatose patients after cardiac arrest, treated with hypothermia, were included within twelve hours after the arrest to undergo continuous EEG monitoring on the intensive care unit. Monitoring continued until patients regained consciousness, died, or up to five days. For this study, the institutional review board waived the need for informed consent.

Second, we identified burst-suppression EEGs from the Medisch Spectrum Twente's, complete hospital database. Here, since January 2005, all EEGs are systematically categorized. Hence, EEGs that meet the criteria for burst-suppression are labeled as such. We took all EEGs from patients aged 18 years or older, recorded between January 2005 and December 2012 and labeled as "burst-suppression."

2.2. EEG recordings

For all recordings, electrodes were applied according to the international 10/20 system, using 19 channels. Electrode impedances were kept below 5 kΩ. Sampling frequency was set to 256 Hz. A Neurocenter EEG system (Clinical Science Systems, the Netherlands) was used with a TMS-i full band EEG amplifier (TMS international, the Netherlands) or a BrainLab EEG recording system (OSG BVBA, Belgium) was used. Data were stored to disk for off-line analysis.

2.3. Visual analysis of burst-suppression patterns

Burst-suppression was defined as any pattern with high amplitude events (>20 μV) alternated with periods of low (<10 μV) or absent EEG activity of at least one second. After visual identification of burst-suppression patterns, these were visually sub-classified into patterns with identical bursts and patterns without identical bursts. Bursts were considered identical, if the first 500 ms were identical, irrespective of amplitude or subsequent duration of bursts or inter-burst intervals.

Of comatose patients after cardiac arrest, this visual analysis was done independently by two investigators (MT-C, MvP) in automatically selected epochs of five minutes at 12 and 24 h after cardiac arrest. These investigators were blinded for the patients' clinical condition during the registration, the recording time of the epoch, and the patient's outcome. In case of disagreement, the final classification was decided by consensus in consultation with a third observer (JH), who had access to the complete recordings, but was blinded for the patients' outcome. All EEG analyses were done after the registrations and EEG played no role in initial treatment decisions.

All other burst-suppression EEGs from the hospital data base were reviewed by a single observer (MvP), blinded for the underlying condition and the patient's outcome.

2.4. Quantitative analysis of burst-suppression patterns

Quantitative analysis of correlation between shapes of subsequent bursts, burst amplitudes, and durations of the interburst intervals was done for EEGs from comatose patients after cardiac arrest. For this purpose, the initiation of 50 subsequent bursts was annotated manually in a particular bipolar channel in each EEG. This was typically done at twelve or 24 h after the arrest. Correlations between the burstshapes (truncated to a duration of $M = 127$ samples i.e. 500 ms) were calculated using the cross-correlation over a range of lags (from $-$maxlag to maxlag, with maxlag = $M-1$). Subsequently, the maximum value of the $2 * \text{maxlag} + 1$ values was determined. This resulted in 1225 different correlations for each patient, from which the mean correlation coefficient per patient was determined. In addition, the mean and maximum amplitude of the first 500 ms of the 50 bursts were calculated. Inter-burst intervals were defined by the time difference between the initiation of bursts. All routines were implemented in Matlab.

2.5. Treatment

Comatose patients after cardiac arrest were treated according to current standard therapy, as described previously (Cloostermans et al., 2012). In short, hypothermia of 33 °C was induced as soon as possible after the arrest and maintained for 24 h by intravenously administered cold saline and cooling pads. Propofol was used for sedation to a level of -4 or -5 at the Richmond Agitation Sedation Scale and discontinued after normothermia had been reached, if possible. Fentanyl or Remifentanil was used against shivering. Of patients other than those included in the prospective cohort study, medication during the registration was not prospectively collected.

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2.6. Outcome assessment

Of comatose patients after cardiac arrest, that had been included in our prospective cohort study, outcome assessment was done at three and six months by telephone (MT-C). The primary outcome measure was the best score on the Cerebral Performance Category (CPC) within six months dichotomized between "good" (CPC 1 or 2) and "poor" (CPC 3, 4, or 5). Secondary outcome measures included mortality (Cloostermans et al., 2012). Of patients other than those included in the prospective cohort study, outcome was not prospectively assessed.

2.7. Statistical analysis

From all patients with burst-suppression EEGs, the proportions of burst-suppression patterns with and without identical bursts were calculated for each underlying condition. All further analyses were done for the subgroup of patients that had been included in our cohort study on the diagnostic value of continuous EEG in comatose patients after cardiac arrest. Inter-observer agreement for the appointment of "identical bursts" between the two independent observers was analyzed with Cohen's Kappa. Identical burst-suppression patterns were compared with other burst-suppression patterns with regard to clinical outcome and quantitative EEG characteristics (bilateral synchrony, amplitude, duration of inter-burst intervals, and correlation of burstshapes). Data are presented as proportions, or means ± standard deviations (SD). Between-group differences were analyzed with Fisher's exact or Student's *t*-test, if appropriate. For burst-suppression with or without identical bursts, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the prediction of poor outcome were calculated, including corresponding 95% confidence intervals (CIs).

3. Results

3.1. Incidence of burst-suppression with identical bursts

From our cohort of 101 comatose patients after cardiac arrest, 48 (48%) had burst-suppression patterns at twelve or 24 h. Twenty (20%) had burst-suppression with identical bursts on visual analysis. Of all other 9600 EEGs in our database, 192 showed burst-suppression. Underlying conditions varied. Two had diffuse cerebral ischemia from other causes than cardiac arrest, both with identical bursts. Burst-suppression with identical bursts was not seen in the six patients with other pathology than cerebral ischemia, or in the 183 patients under anesthesia (Table 1). Three examples of burst-suppression without identical bursts are shown in Fig. 1, and three examples of burst-suppression with identical bursts in Fig. 2.

Table 1
Causes of burst-suppression patterns with and without identical bursts.

Cause of burst-suppression	Identical bursts	
	Yes	No
Cerebral ischemia		
Coma after cardiac arrest	20	28
Drowning	1	
Hanging	1	
Cerebral infarction		1
Other causes		
Traumatic brain injury		3
Therapeutic hypothermia		1
Propofol or sevoflurane anesthesia		183
Meningitis		1
Craniotomy		1
Total	22	218

3.2. Timing of burst-suppression with identical bursts

Baseline characteristics of comatose patients after cardiac arrest with burst suppression are summarized in Table 2. In these patients, burst- suppression with identical bursts was observed between a median of 12 (range 3–23) and 36 (range 15–53) hours after the arrest. These patterns were followed by burst-suppression without identical bursts in twelve patients (60%, subsequently low voltage in four), generalized periodic discharges in four (20%), epileptic discharges in one (5%), and low voltage in one (5%). In two patients, burst-suppression with identical burst was present up to death. Burst-suppression without identical bursts disappeared more gradually after approximately median 32 (range 17–72) hours after cardiac arrest. This pattern was followed by continuous slowing in 22 patients (79%, subsequently generalized periodic discharges in seven), generalized periodic discharges is three (11%), and low voltage in one (4%). In one patient, burst-suppression without identical burst was present up to death.

3.3. Inter-observer agreement

Cohen's Kappa for inter-observer agreement of identical vs. non-identical bursts was 0.8. Disagreement always resulted from selection of the observed epoch: either the inter-burst interval was longer than five minutes, so that bursts fell outside the epoch, or bursts were only partly represented within the epoch. Consensus was always readily reached by looking outside the epoch.

3.4. Quantitative analysis

Quantitative EEG characteristics of comatose patients after cardiac arrest with burst-suppression with and without identical bursts are illustrated in Figs. 1 and 2 and summarized in Table 3. Burst-suppression with identical bursts was more often bilateral synchronous than burst-suppression without identical bursts, amplitudes were higher, and correlation coefficients of burstshapes were higher. The only patient with identical bursts according to visual analysis, who still had a correlation coefficient lower than 0.75, had identical bursts of very short duration (~200 ms). In this patient, the time interval in which correlation was determined (500 ms) was probably too long to adequately measure correlation coefficients between the bursts. Although quantitative analysis was restricted to the first 500 ms, visual analysis revealed identical burstshapes extending beyond 500 ms, in bursts with durations longer than 500 ms. In burst-suppression with identical bursts, the interburst-intervals were invariably flat and all transitions between bursts and interburst-intervals were abrupt.

3.5. Outcome

All twenty patients with identical bursts (100%) had a poor outcome vs. ten (36%) without identical bursts. Patients with a poor outcome never regained consciousness and all died. Sensitivity, specificity, PPV, and NPV of burst-suppression with and without identical bursts based on visual analysis for prediction of poor outcome are given in Table 4.

4. Discussion

We report on a distinct EEG burst-suppression pattern, which we propose to label "burst-suppression with identical bursts." This pattern was present in twenty percent of our patients after diffuse cerebral ischemia, but was not seen in the six patients with other pathology than cerebral ischemia, or in the 183 patients under anesthesia. In burst-suppression with identical bursts, burstshapes

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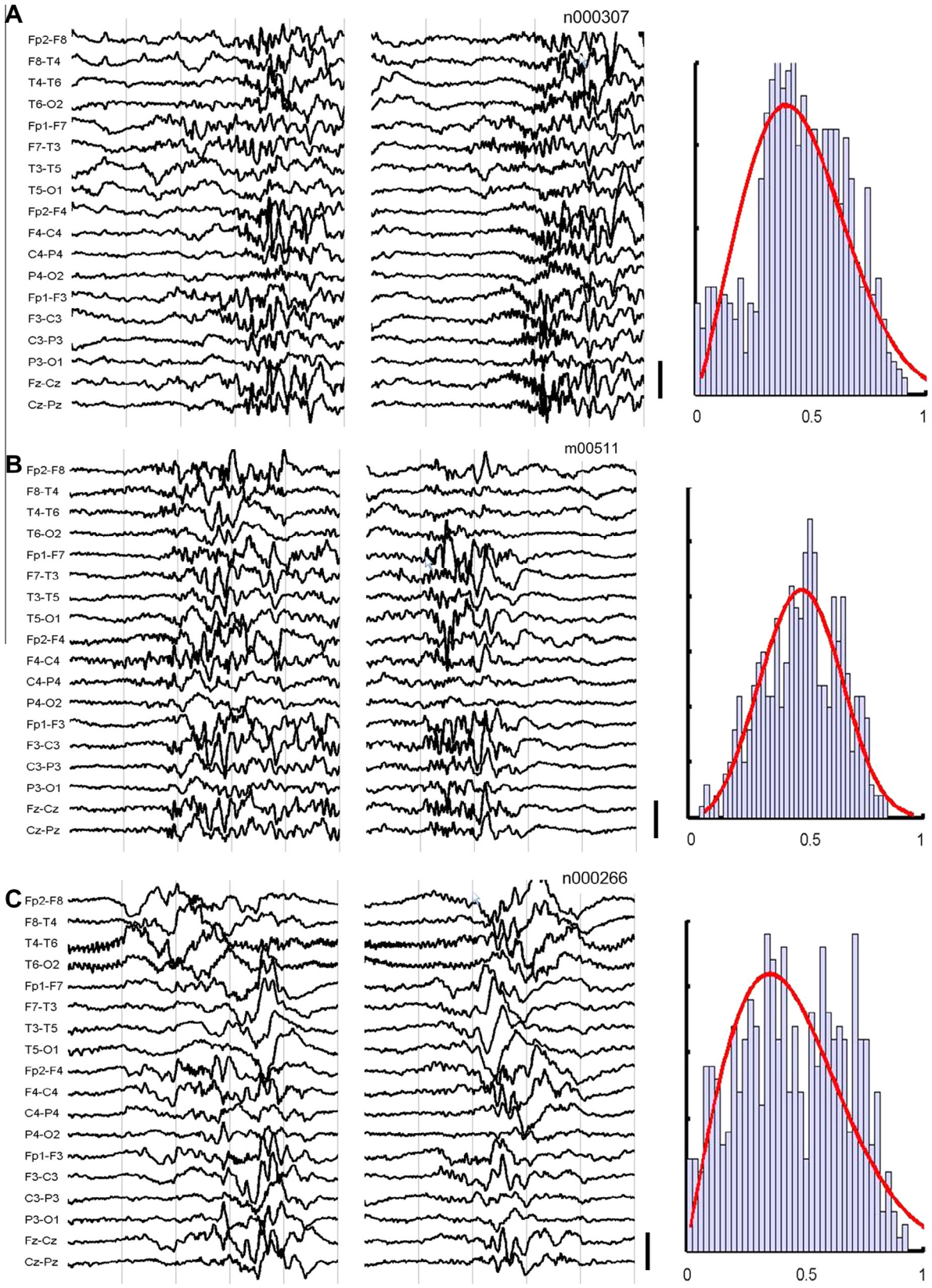

Fig. 1. Left panels: illustration of EEGs of three comatose patients after cardiac arrest (A–C) showing "common" burst-suppression, without identical bursts. These patients were sedated with propofol 1–2.5 mg/kg/h. The individual EEG epochs have a duration 5 s. The mean interburst interval is 5.0 s (A), 9.8 s (B), or 11.8 s (C). Vertical bar: 100 μV. Filter settings 0.5–25 Hz. Right panels: histograms of correlation coefficients of burst-shape (r): in all three patients $r < 0.75$.

are highly similar and bilateral synchronous. Inter-burst intervals are variable in duration and invariably flat. Inter-observer agreement of identical vs. non-identical bursts was high ($\kappa = 0.8$), and disagreement always resulted from sampling error. All patients with burst-suppression with identical bursts, but not all patients with other burst-suppression patterns, died. This indicates that

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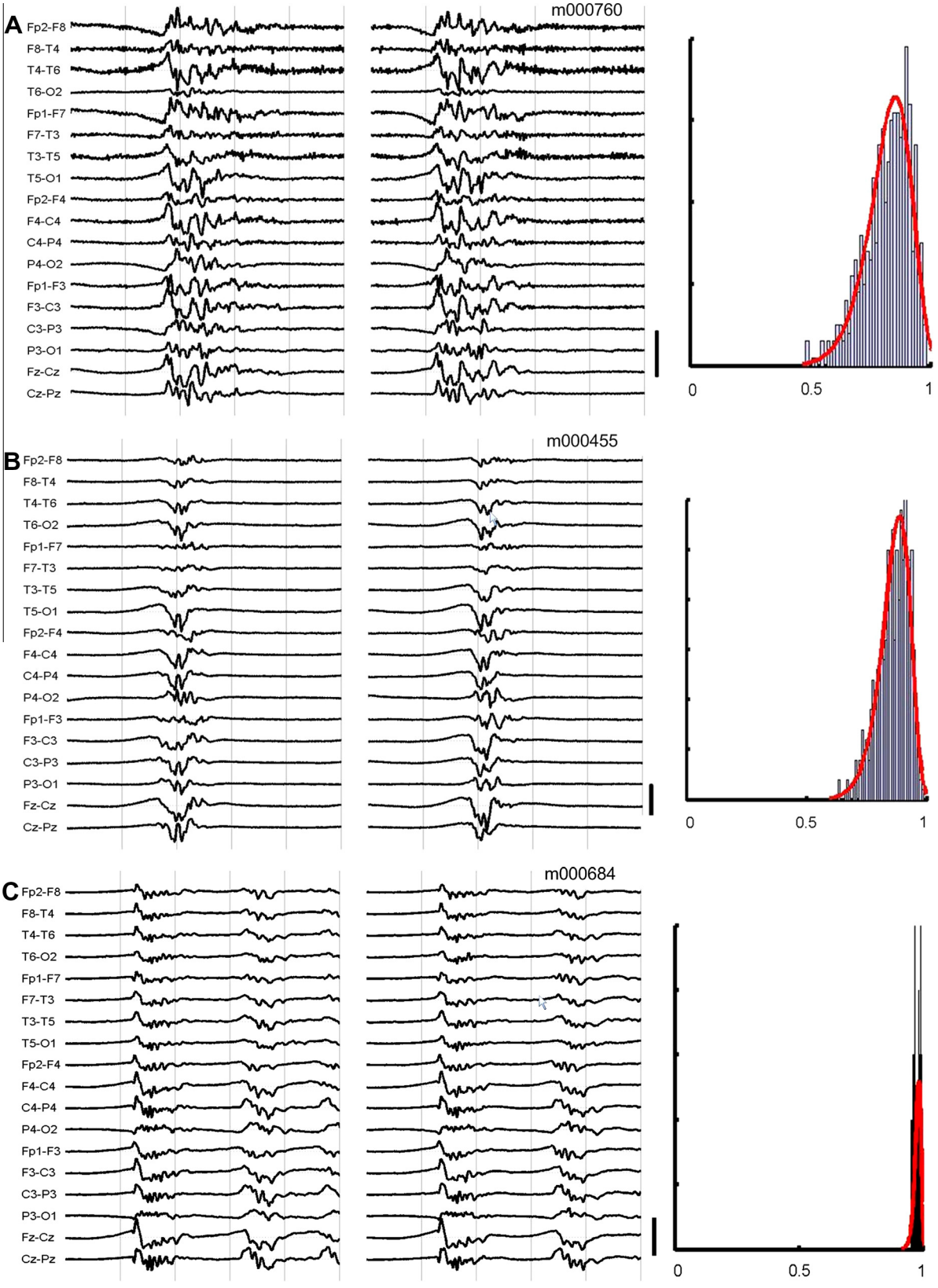

Fig. 2. Left panels: illustration of EEGs of three comatose patients after cardiac arrest (A–C) showing "burst-suppression with identical bursts." (A) Recording from an eighty years old patient sedated with propofol 1–2.5 mg/kg/h; inter-burst interval 19 ± 9 s. (B) 80 years old patient sedated with propofol 1–2.5 mg/kg/h; inter-burst interval 65 ± 64 s. (C) 68 years old patient without sedative medication at normothermia inter-burst interval 60 ± 23 s. The correlation extends over more than three seconds. The individual EEG epochs have a duration of 5.0 s. Vertical bar: 100 μV. Filter settings 0.5–25 Hz. Right panels: histograms of correlation coefficients of burst-shape (r): in all three patients $r > 0.85$.

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Table 2
Baseline characteristics of comatose patients after cardiac arrest with burst-suppression EEG with and without identical bursts.

	Identical bursts		*P* value
	Yes (n = 20)	No (n = 28)	
Age (years)	67	65	0.8
OHCA	17 (85%)	25 (89%)	0.7
Presumed cause of cardiac arrest			0.1
Cardiac	10 (50%)	20 (71%)	
Other	6 (30%)	2 (7%)	
Unknown	4 (20%)	6 (22%)	
Initial rhythm			0.02
VF	8 (40%)	21(75%)	
Asystole	8 (40%)	2 (7%)	
Bradicardia	3 (15%)	2 (7%)	
Unknown	1 (5%)	3 (11%)	
Propofol treatment	19 (95%)	28 (100%)	0.4
Propofol dosage (mg/kg/h)	2.5 ± 1.2	3.2 ± 1.2	0.05
Midazolam treatment	2 (10%)	6 (21%)	0.4
Midazolam dosage (μg/kg/h)	4.1 ± 12.6	11.9 ± 26.4	0.2
Fentanyl treatment	10 (50%)	24 (86%)	0.01
Fentanyl dosage (μg/kg/h)	0.9 ± 1.2	1.4 ± 0.8	0.06
Remifentanil treatment	10 (50%)	5 (18%)	0.03
Remifentanil dosage (μg/kg/h)	3.9 ± 2.2	5.2 ± 3.9	0.4

OHCA indicates out of hospital cardiac arrest; VF, ventricular fibrillation; dosage, maximum dosage within the first 24 h.

Table 3
Characteristics of (patients with) burst-suppression with and without identical bursts.

	Identical bursts on visual analysis		
	Yes (n = 20)	No (n = 28)	*P* value
Mortality	20 (100%)	10 (36%)	<0.0001
Bilateral synchrony	20 (100%)	18 (64%)	0.03
Mean amplitude (μV)	26.4 ± 16.0	6.5 ± 3.8	<0.0001
Maximal amplitude (μV)	127.8 ± 104.5	24.9 ± 14.2	0.0001
Mean inter-burst intervals (s)	53 ± 58	76 ± 339	0.8
Mean correlation coefficient of burstshape	0.85 ± 0.08	0.49 ± 0.08	<0.0001
Correlation coefficient of burstshape >0.75	19	0	<0.0001

In number (%) of patients or mean ± standard deviation. Amplitude indicates amplitude in the first 500 ms of the burst.

burst-suppression with identical bursts represents irreversible ischemic network damage of the brain predicting poor outcome with a specificity and PPV of 100%.

Burst-suppression patterns are characterized by oscillations with two time scales: a fast time scale for the intra-burst oscillations and a slow time scale for the periods between the bursts (Izhikevich, 2007; van Putten and van Putten, 2010). The burst initiation and termination are the result of bifurcations in the system: a bifurcation of an equilibrium attractor, resulting in a transition from resting to bursting, followed by a bifurcation from a limit cycle attractor back to the resting state (Izhikevich, 2007; van Putten and van Putten, 2010). During the bursting, with fast time-scale activity, there must also be a relatively slow process making neurons inexcitable (van Putten and van Putten, 2010).

In most situations, these two time scales result from processes involving fast and slow ion currents. An example is the slow activation of the Ca^{2+} dependent K^+ after-hyperpolarizing current (I_{AHP}). This current is activated during bursting (fast time scale), as the intracellular Ca^{2+} concentration increases, and eventually results in ending of the burst. Hereafter, the intracellular Ca^{2+} is slowly removed and bursting may start again, as the outward K^+ current deactivates. Other scenarios include a calcium mediated inactivation of an inward current and voltage gated inactivation of inward, or activation of outward currents. These and other mechanisms are discussed in more detail in (Izhikevich, 2007). Although such processes may result in identical burst morphology in single neurons, it is not straightforward how identical bursts arise at the spatial scale of an EEG.

Ching et al. proposed unifying mechanisms for all burst suppression patterns: an imbalance of neural activity and available energy (Ching et al., 2012). However, both our observed burst phenomenology and the assumed pathophysiology of underlying conditions argue against the same mechanism for burst-suppression patterns from different causes. With regard to burst phenomenology, Ching's simulations generated variable bursts with equal (physiological) spectral content as in baseline EEG, with preservation of dominant power in the α frequency band. Otherwise, the spectral contents of our EEGs with "burst suppression with identical bursts" consist of frequencies ranging from the β to δ band, without a clear dominant frequency. Therefore, their claim that their model is consistent with descriptions of burst-suppression in ischemic brain injury is not substantiated by our findings.

With regard to pathophysiology, the initial event in cerebral ischemia is synaptic failure (Bolay et al., 2002; Hofmeijer and van Putten, 2012) where excitatory synapses are more vulnerable than inhibitory (Dzhala et al., 2001). As energy levels further decrease, Na^+/K^+ pumps will fail and neurons will depolarize (Rabinovici et al., 2000; Xu and Pulsinelli, 1994; Zandt et al., 2011). In contrast, during medication induced burst-suppression, neurons have been shown to hyperpolarize (Steriade et al., 1994), which has been ascribed to depression of glutamate mediated excitatory post-synaptic currents (Lukatch et al., 2005). Furthermore, identical bursts in burst suppression typically occurred one to two days after the cardiac arrest, and continued during hours up to days. Since blood flow has been restored at this time, an absolute lack of energy is unlikely.

Burst-suppression with identical bursts suggests a deterministic process of burst generation, whereas other burst-suppression patterns rather depend on stochastic processes. In a previous report, we have shown that bursts-suppression with identical bursts represents a low dimensional state (van Putten and van Putten, 2010). In patients after diffuse cerebral ischemia, selective synaptic failure is a candidate mechanism for this condition, since during cerebral ischemia synaptic function fails before the occurrence of membrane depolarization (Hofmeijer and van Putten, 2012). This may result in deterministic network behavior of the brain, especially since gap junctions are expected to be preserved (Talhouk et al., 2008). Synaptic disturbances are presumably

Table 4
Sensitivity, specificity, and predictive values of burst-suppression with or without identical bursts within 48 h after cardiac arrest for prediction of poor outcome.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Burst-suppression with identical bursts	40% (27–55%)	100% (91–100%)	100% (80–100%)	63% (51–73%)
Burst-suppression without identical bursts	20% (11–34%)	65% (50–77%)	36% (20–56%)	45% (34–57%)

Burst-suppression with or without identical bursts has been identified visually; 95% CI indicates 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value.

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irreversible after relatively severe ischemia, which may explain the high case fatality rate of patients with burst-suppression with identical bursts (Bolay et al., 2002; Hofmeijer and van Putten, 2012). Imaging techniques, such as MRI, may not detect such irreversible network damage, as synaptic changes need not to be accompanied by cell swelling (Bolay et al., 2002; Hofmeijer and van Putten, 2012), which is supported by the finding that approximately 20% of patients with a poor neurological outcome after diffuse cerebral ischemia had no abnormalities on early MRI (Mlynash et al., 2010).

Burst-suppression has been associated with poor neurological outcome of survivors of cardiac arrest before. However, in previous studies, predictive values were much lower than 100% (Cloostermans et al., 2012; Lee et al., 2010; Rossetti et al., 2010; Wijdicks et al., 2006). In these studies, patterns were probably heterogeneous, including burst-suppression with and without identical bursts, supporting the notion of identical bursts being a distinct characteristic. Furthermore, the current study confirms our previous results with regard to timing: specific EEG changes only have a high predictive value if measured soon after cardiac arrest (Cloostermans et al., 2012). After a median of 36 h, burst-suppression with identical bursts evolves into less specific pathological patterns.

Differences in baseline characteristics of patients with and without identical bursts include the initial rhythm before resuscitation, propofol dosages, and proportions of patients treated with fentanyl or remifentanil. Ventricular fibrillation occurred more often in patients with identical bursts. This is inconsistent with our finding of poorer outcome in patients with as compared with those without identical bursts, since ventricular fibrillation is associated with a better outcome after resuscitation as compared with asystole or bradycardia (Pleskot et al., 2009). The lower dosages of propofol and the smaller proportions of patients treated with fentanyl or remifentanil in patients with as compared to those without identical bursts probably reflects more severe ischemic cerebral damage, in which less sedative medication was needed during ventilation and hypothermia.

Our study has certain limitations. First, some comatose patients after cardiac arrest did not die as a result of cerebral damage, but from other complications. It cannot be excluded that neurological recovery would have occurred in these patients. Second, it was a single center study, which may have influenced treatment decisions or EEG analysis. Third, most recordings of burst-suppression with identical bursts after cardiac arrest were during treatment with propofol. However, the observed identical burst-suppression patterns cannot be solely caused by this drug. Propofol induced EEG changes are well known. In the relatively low dosages that were used in our patients, the EEG remains continuous, with anteriorization of the "alpha" rhythm (Hindriks and van Putten, 2012). If burst-suppression is induced by propofol, bursts are heterogeneous and appear and disappear gradually (Kusters et al., 1998; Reddy et al., 1992), whereas our identical burst-suppression patterns were all characterized by abrupt transitions between bursts and suppressions. Moreover, several of our patients with burst-suppression with identical bursts were not medically sedated and two previously reported patients were neither treated with any sedative medication (Hughes, 1986). Fourth, data on EEG reactivity, brainstem reflexes, and clinically overt myoclonia were not collected prospectively, and retrospective collection appeared unreliable. Therefore this information is lacking.

5. Conclusion

Burst-suppression with identical bursts is a distinct pathological EEG pattern that in our series only occurred after diffuse cerebral ischemia. In comatose patients after cardiac arrest, it was invariably associated with poor outcome.

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