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Burst-suppression is reactive to photic stimulation in comatose children with acquired brain injury

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H I G H L I G H T S

- In comatose children, the EEG burst ratio increases during photic stimulation.
- Burst ratio reactivity, the degree of change in the burst ratio during photic stimulation, correlates with the Glasgow Coma Scale score.
- Burst ratio reactivity may represent a simple tool to monitor coma severity in critically ill children.

A B S T R A C T

Objective: Burst-suppression is an electroencephalographic pattern observed during coma. In individuals without known brain pathologies undergoing deep general anesthesia, somatosensory stimulation transiently increases the occurrence of bursts. We investigated the reactivity of burst-suppression in children with acquired brain injury.
Methods: Intensive care unit electroencephalographic monitoring recordings containing burst-suppression were obtained from 5 comatose children with acquired brain injury of various etiologies. Intermittent photic stimulation was performed at 1 Hz for 1 min to assess reactivity. We quantified reactivity by measuring the change in the burst ratio (fraction of time in burst) following photic stimulation.
Results: Photic stimulation evoked bursts in all patients, resulting in a transient increase in the burst ratio, while the mean heart rate remained unchanged. The regression slope of the change in burst ratio, referred to as the standardized burst ratio reactivity, correlated with subjects' Glasgow Coma Scale scores.
Conclusions: Reactivity of the burst-suppression pattern to photic stimulation occurs across diverse coma etiologies. Standardized burst ratio reactivity appears to reflect coma severity.
Significance: Measurement of burst ratio reactivity could represent a simple method to monitor coma severity in critically ill children.

1. Introduction

It has long been observed experimentally that with increasing depth of anesthetic coma, the electroencephalogram (EEG) becomes discontinuous (Derbyshire et al., 1936). This EEG pattern was later termed "burst-suppression" (BS) (Swank and Watson,

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1949). Electrographically, BS consists of a quasi-periodic alternating pattern of epochs of high amplitude (75–250 μV) bursts of sharply contoured polyphasic slow-waves and/or spike and slow-waves in the delta (0.5–4 Hz) and theta (4–7 Hz) ranges, and epochs of fully suppressed low-amplitude EEG with average amplitudes below 5 μV. Previous experimental studies and human neurophysiological studies concluded that BS patterns are cortically generated and occur in disconnected and/or disrupted cortical networks either by pharmacological or anatomical methods (Henry and Scoville, 1952; Fischer-Williams, 1963; Steriade et al., 1994; Timofeev et al., 2000; Lukatch et al., 2005).

BS is commonly seen in children when medically induced coma is used either as a neuroprotective strategy following traumatic brain injury or in children with refractory status epilepticus. It is usually considered by clinicians to be an unresponsive and unexcitable brain state associated with deep coma. Nevertheless, prior experimental data suggest that although BS reflects an exceptionally profound level of depressed consciousness, BS patterns can be modulated by external stimuli (Hartikainen et al., 1995a,b; Hudetz and Imas, 2007). More recently it was suggested that BS may even represent a hyperesponsive brain state (Kroeger and Amzica, 2007) during which even subliminal stimuli are able to evoke bursts.

The burst-suppression ratio, or simply suppression ratio (SR), defined as the relative time spent in suppression, was found to increase monotonically with anesthetic concentrations (Rampil et al., 1988; Rampil and Laster, 1992). A simple binary feature reduction (burst-no burst) proved sufficient to describe the "depth of coma" from otherwise extremely complex BS signals (Bruhn et al., 2000; Kreuer et al., 2004; Liberman et al., 2013). We recently found that in adults undergoing general anesthesia, repetitive somatosensory stimulation causes a transient change in the SR, which we termed *BS reactivity* (Calin et al., 2014). Nevertheless, when using this terminology, increased reactivity is associated with a larger reduction in SR which could be counter-intuitive. To better reflect the physiological phenomenon, here we introduce instead the new term of burst ratio (BR) defined as 100-SR: A BR of 0% identifies full suppression.

The aim of this study was to investigate the reactivity of BS among children with severe acquired brain injury by measuring the change in BR during photic stimulation, and to explore whether this BR reactivity may represent a marker of coma severity.

2. Methods

2.1. Study population

We retrospectively identified 5 comatose children using the EEG database of The Hospital for Sick Children (Toronto, Canada) who were admitted to the Pediatric Intensive Care Unit (PICU), underwent continuous EEG (cEEG) monitoring, presented with BS at the onset of the EEG recording, and in whom photic stimulation (PS) was employed as a standard activation procedure in order to assess EEG background reactivity. Demographic characteristics are given in Table 1. Two subjects were male, and the mean age was 12.3 ± 4.7 years, (range 3.5–17 years). The Glasgow Coma Scale (GCS) scores documented before sedation for transport or intensive care were retrieved by chart review from local hospitals, emergency records and admission notes (Gill et al., 2005). The GCS scorer was blinded to the results of EEG analysis. The study was approved by the hospital's Research Ethics Board and a waiver of informed consent was granted (Protocol # 1000020096).

2.2. Continuous EEG and ECG recordings

cEEGs were performed using Stellate VITA portable digital EEG recorders (Natus Medical Incorporated, San Carlos, CA). Twenty-one surface electrodes were applied according to the 10–20 International System at Fp2, Fp1, F8, F7, F4, F3, A2, A1, T4, T3, C4, C3, T6, T5, P4, P3, O2, O1, Fz, Cz and Pz and EEG was recorded against a Pz′ reference. We used gold electrodes, fixed with conductive paste. Electrode impedance was below 5 kΩ at the start of the recording. A one-lead ECG was recorded in parallel with the EEG. The signals were sampled with a rate of 200 Hz and a 16 bit analog–digital voltage resolution, then filtered between 1 and 70 Hz. During monitoring the electrodes were inspected at least once daily.

2.3. Photic stimulation paradigm

PS was performed daily to evaluate EEG background reactivity. Stroboscopic flashes (LED photic stimulator, Natus Medical Incorporated, San Carlos, CA) were applied at a frequency of 1 Hz. The target duration of PS was 60 s, although some variation occurred (Table 1). All PS sessions were repeated following a rest period of at least 3 min.

2.4. EEG analysis

The EEG was automatically segmented as follows to include the 60-s epoch prior to PS and the 60-s epoch after PS, referred to as "Pre", "Stim" and "Post" respectively (Fig. 1A). The multichannel EEG was rectified, normalized and thresholded to obtain the multichannel binary BS signal as described in detail in our previous rat (Constantinescu et al., 2011) and human studies (Calin et al., 2014; Moldovan et al., 2016).

The included patients did not have any clinical reasons to suspect an asymmetric BS (Table 1). However, in high-density cortical recordings the binary BS signal has been found to be asymmetric (Lewis et al., 2013). Although we recently reported that this was unlikely to influence the BS signals derived from surface EEG recordings (Moldovan et al., 2016), automatic thresholding of BS itself could be influenced by recording position (Jingzhi et al., 2015), especially in our case when the occipital visual evoked potentials (VEPs) generated during flash could be added to the detected burst. To address these potential confounders we carried out a topographic analysis of BS distribution using a variation of the '*topoplot()*' function from the EEGLAB (Delorme and Makeig,

Table 1
Characteristics of comatose children with acquired brain injury.

Patient	Sex	Age (years)	Diagnosis	GCS	Number of PS sessions (total)/reliable ECG epochs	PS duration mean (range), s
P1	M	3.5	SE, mitochondrial disease	9	9/4	64 (9–92)
P2	F	12	SE, FIRES	12–13	7/5	31 (29–36)
P3	F	16	SE, anti-NMDAR encephalitis	8–9	7/5	62 (57–79)
P4	F	13	SE, FIRES	13–14	4/3	59 (57–59)
P5	M	17	BS after AVM rupture	7	5/2	61 (58–71)

BS, burst suppression; GCS, Glasgow Coma Scale (1–15); PS, photic stimulation; SE, status epilepticus; FIRES, febrile infection related epilepsy syndrome; NMDAR, *N*-methyl-D-aspartate receptor; AVM, arteriovenous malformation.