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Review

What does burst suppression really mean?

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ABSTRACT

This paper describes the various electroencephalographic (EEG) patterns expressed by the comatose brain, starting with the sleep-like oscillations associated with light coma. Deeper coma generally displays a burst-suppression pattern characterized by alternating episodes of isoelectric (flat) EEG and bursting slow waves. The latter are the result of cortical hyperexcitability, as demonstrated by intracellular recordings in anesthetized animals. Further deepening of the coma yields to continuous isoelectric electroencephalogram and eventually results in a newly discovered type of spiky waves that have been termed Nu-complexes. The paper discusses the structures participating in the genesis of burst suppression, the afferent mechanisms, and the reasons for which this activity should or should not be regarded as an epileptic disorder.

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1. Introduction

The term burst suppression describes an electroencephalographic (EEG) pattern consisting of a continuous alternation between high-voltage slow waves (occasionally sharp waves) and depressed (or suppressed) electrographic activity. This pattern was described by Derbyshire and colleagues in association with various anesthetics [1], while the term burst suppression was later introduced by Swank and Watson to emphasize the alternating aspect of the electroencephalogram [2]. From the beginning, burst suppression was noticed in various conditions, such as isolated cerebral cortex [3], coma with dissolution of cerebral functions [4], trauma with cerebral anoxia [5], or infiltrating cortical tumors [6]. In addition, burst suppression appears during deep coma consequent to cardiac arrest [7,8], drug intoxications [9–11], encephalopathies [12,13], or hypothermia [14–16]. This etiological heterogeneity yielding to more or less the same EEG pattern (see, however, ref. [17]) has nurtured through times a certain ambiguity with respect to the interpretation of pathophysiological mechanisms underlying burst suppression.

The cyclic occurrence of high amplitude EEG bursts, with possible sharp waves, lies at the very core of placing burst suppression in one of the possible categories of a status epilepticus. In order to justify this statute, however, several questions need to be answered.

2. What is the behavioral dynamic range to which burst suppression belongs?

In all cases mentioned above, burst suppression is associated with a profound obliteration of consciousness and develops in parallel with increased levels of the causal factor (e.g., increased concentrations of the drug/anesthetic and increased hypoxia). In all these cases, loss of consciousness occurs gradually and prior to the actual onset of burst suppression. Loss of consciousness is accompanied, at the EEG level, by slow ample waves containing increasing amounts of delta (<4 Hz) activity (Fig. 1B). Up to this point, the progression of coma parallels the deepening of natural slow wave sleep (SWS).

Further worsening of the comatose state initially brings short periods with suppressed EEG interrupting almost continuous slow waves. Eventually, suppressions become progressively longer and the slow waves become clustered in shorter bursts (Fig. 1C). Burst suppression can further decline to a state with almost continuous isoelectric line interrupted occasionally by scattered bursts.

If coma deepens, it reaches a state in which the EEG displays a continuous isoelectric line (Fig. 1D). Until recently, this was considered to be the last frontier of a living brain and was (in some countries still is) one of the criteria for establishing brain death. However, we have discovered that, under particular conditions (see below), a brain with intact cellular elements can undergo a far deeper comatose state, eliciting a regain of EEG activity with characteristic waves that we have called Nu-complexes (Fig. 1E) [18].

This progression of the brain from wakefulness with preserved consciousness towards extremely deep coma has been obtained by using well-controlled increments of isoflurane, a halogenated anesthetic [19] with neuroprotective properties [20,21] that modulates hemodynamic

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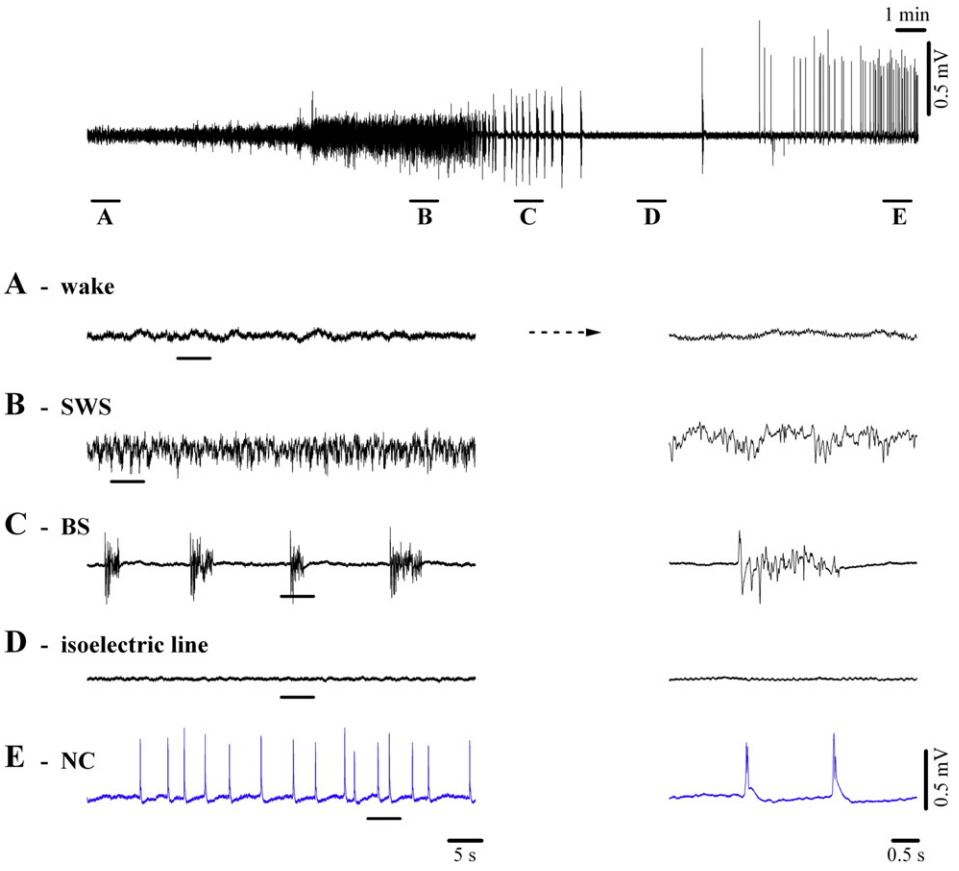

Fig. 1. EEG patterns during wakefulness and various degrees of loss of consciousness. EEG recording in a cat during application of various concentrations of isoflurane (IF). The panel above depicts the complete sequence, the underlined epochs are expanded below and, for each line, a further detail is shown to the right. A: undrugged preparation displaying low amplitude, fast (mostly >15 Hz) EEG. B: slow-wave sleep-like (SWS) pattern after 1% IF; higher amplitude slow waves dominated by delta oscillations (<4 Hz). C: burst suppression (BS) induced with 2% IF showing alternative isoelectric lines and bursting episodes. The latter are very similar with the SWS pattern (see detail at right). D: further increase of IF concentration (3%) leads to stable isoelectric line characterized by the absence of phasic events. Very low-amplitude activities can be seen at high gain. E: IF at 4% elicits a revival of quasirhythmic spiky potentials of high amplitude, which we called ν-complexes (or Nu-complexes; NC).
Modified from [18].

parameters by increasing cerebral blood flow through vasodilation [22]. In other words, comas with different etiologies might not preserve the cellular integrity of cerebral structures and would, therefore, result in cellular damage. In such cases, the evolution is similar (slow-wave sleep-like waves, burst suppression), but most of the time, the isoelectric line represents the last frontier before cerebral death.

However, regardless of etiology, burst suppression represents a behavioral state situated between continuous slow-wave sleep-like EEG and isoelectric EEG. One of the most challenging tasks for a clinician is to precisely frame the state of a comatose brain and to make an educated guess as to its dynamic evolution. Continuous EEG monitoring might be, thus, an invaluable assisting tool since a comatose brain may continuously slide between states as a function of the evolution of the insult and/or of the treatment.

3. Which structures and/or cellular mechanisms are involved in the genesis of burst suppression?

The understanding of the cellular mechanisms responsible for the genesis of the burst-suppression pattern is important, among others, for the correct interpretation of the EEG waveforms. In a first approach, I would emphasize that the EEG, especially when recorded from the scalp, generally reflects the activity of cortical dipoles (see [23]). Thus, it is generally safe to assume that suppression (isoelectric) episodes in the EEG reflect cortical silence but do not constitute an absolute indication of neuronal loss/death and, more importantly, do not guarantee that subcortical structures are silent, as well.

In fact, it has been demonstrated that dorsal thalamic neurons display tonic and rhythmic activities between bursts, and these discharges can be modulated by sensory stimulation [24]. More recently, we have shown that hippocampal neurons constitute a source of ongoing oscillations during isoelectric EEG [18]. At the more superficial entrance into burst-suppression coma, the frequency of these hippocampal oscillations belongs to the alpha–beta band (Fig. 2B1) and continuously slows down to the delta range as coma deepens (Fig. 2B2–4).

Electroencephalographic studies have shown that functional or anatomical impairment of cortical afferents leads to burst suppression [3,13,25], which corroborates with the idea that bursts generators are within the cortex [26]. The first study of cellular correlates of burst suppression has indeed shown that the bursting EEG activity reflects slow activity of cortical neurons [24]. These neurons display excitatory activity, occasionally crowned by action potentials in tight synchrony with field potentials and EEG waves. The strong correlation between intraneuronal and EEG activities suggests that most, if not all, cortical neurons are synchronized during bursts. This is important to be emphasized because, up to that point, the extent of synchronization was evaluated based only on EEG (see for example refs. [27,28]). It is known that because of the dipolar nature of the EEG [23] and the fact that cortical dipoles, normally oriented on the surface of sulci, point towards other areas of the brain, including the contralateral hemisphere, the evaluation of synchrony based on EEG recordings generally represents an overestimation.

Recently, we have found that the burst suppression induced with various anesthetics (isoflurane, propofol, barbiturates) is associated