

Mechanism of Burst-Suppression During General Anesthesia: Review of Narrative Literature

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To cite this article:

Halladain Mpung Mansoj, Anna Modji Basse, Adjaratou Dieynabou Sow. (2024). Mechanism of Burst-Suppression During General Anesthesia: Review of Narrative Literature. *Clinical Neurology and Neuroscience*, 8(1), 1-7. <https://doi.org/10.11648/j.cnn.20240801.11>

Received: October 3, 2023; **Accepted:** November 1, 2023; **Published:** January 8, 2024

Abstract: Burst suppression is an electroencephalography pattern that is characterized by periods of high-voltage electrical activity alternating with periods of no activity in the brain. The pattern is found in patients with inactivated brain states, such as from general anaesthesia, coma, or hypothermia. The pseudo-rhythmic pattern of burst suppression is dictated by extracellular calcium depletion and the ability of neurons to restore the concentration. Bursts are accompanied by depletion of extracellular cortical calcium ions to levels that inhibit synaptic transmission, which leads to suppression periods. During suppression, neuronal pumps restore the calcium ion concentrations to normal levels, thus causing the cortex to be subject to the process again. As the brain becomes more inactive, burst periods become shorter and suppression periods become longer. The shortening of bursts and lengthening of suppression is caused by the central_nervous_system's inability to properly regulate calcium levels due to increased blood brain permeability.

Keywords: Burst-Suppression, Electroencephalography Pattern, Cerebral Blood Flow Velocity

1. Introduction

Burst suppression was first discovered [1]. And consists in of the episodes alternate of periods EEG flat isoelectric with of the gusts waves slow, y Understood of the variations systemic And quasiperiodic Or the periods of high tension And isoelectrics exhibit variations between and within bursts [2-6].

There deletion of the gusts has summer identified in hypothermia, the coma, early infantile epileptic encephalopathy and in general anesthesia, the subject of this review [7].

There are many controversies about puff suppression, including Understood her relationship with the delirium postoperative (POD) - the appearance postoperative of a change acute by report has attention of base, there fluctuation of there awareness and the troubles cognitive representative of insufficiency cerebral acute (American Geriatrics Society Expert Panel we Postoperative Delirium in older adults, 2015) [8]. American Geriatrics Society recognizes POD as the most common surgical

complication in the elderly, occurring in up to 50% of patients after intervention surgical. the P.O.D. leads of the stays hospital more long, A need increased of care of long duration, a loss of independence function, reduced cognition, and death [9]. He cost approximately 150 billion of dollars to UNITED STATES each year, even if he is preventable in up to 40% of patients [8]. In addition, the POD leads an increase of cost of the care of health, her prevention has SO summer.

Declared a public health priority; in July 2010, the National Institute for Health and Clinical Excellency has published a line director wearing on the diagnostic, there prevention and there socket in charge of delirium [10]. However, the link between burst suppression and POD remains controversial, and studies have conflicting results. This magazine will explore the methods current used For assess there deletion of the puffs, its origins and proposed mechanisms, the relationship with the results cognitive, the role of medications and associated risk factors, in order to present their understanding current of there deletion of the puffs intraoperative and of its consequences.

The objective of this work was to identify the mechanism of there burst deletion at course anesthesia general.

2. Materials and Methods

A criteria-based narrative systematic literature review PRISMA-P [11] has summer carried out in leaning methodologically on there publication of the article of Zaugg And al [12] as well as the guide to recommendations relating to journals systematic narrative of the *Economic and Social Research Council* (ESRC). [13]

2.1. Basics of Data and Equations Searches

There review of there literature has summer performed in the basics of data international *MEDLINE* and *Cochrane data base of systematic reviews* by their search engine (respectively *PubMed*). The data French speakers were searched with the search engines of the *Database of the Scientific Literature in Health* site (LiSSa), of the *University Documentation System* (SUDoc), the *Catalog and Index sites Medical of language French* (CISMeF).

Gray literature was also integrated using *Google Scholar*. The results have summer enriched by their reading of the references bibliographies of the selected publications. For each search engine research, different equations have summer proposed in order to arrive At the most sensitive result possible without neglecting the criterion of specificity of the results researches.

The international review was carried out using the words of the *Medical Subject Heading* (MeSH) assigned to general medicine. These terms were then combined by the bias of operators booleans (and, or). *MEDLINE* has SO summer.

Interrogates Thus by her engine of research *PubMed*, the algorithm obtained was:

("((Burst [All Fields] AND suppression [All Fields]) AND "anesthesie" [All Fields]) AND mecanismes [All Fields])

((Burst [All Fields] AND suppression [All Fields]) AND ("General anaesthesia"[All Fields] OR "anesthesia, General" [MeSH Terms] OR ("anesthesia" [All Fields] AND "general" [All Fields]) OR "general"

THE *SUDoc* has summer interrogates at through of combinations of words keys specific

("Burst suppression*") et "mécanisme*" et "anesthésie* général*"

THE *CISMeF* and *LiSSa* have summer interviewed according to the equation of research:

Burst suppression and General anesthesia

There literature grey has summer swept via *Google Scholar*:

"Burt suppression" AND mécanisme* AND "anesthésie général"

2.2. Selection of the Studies

2.2.1. Double Blind

THE results products by the app of the equations of research in the different search engines made it possible to obtain a list of publication.

The selection was initially made on the title and the abstract and in a second time on there reading of Full Text.

2.2.2. Criteria Inclusion and Exclusion

THE studies were to be written in language English and French.

Criteria major of inclusion were to be found in the title or the summary:

- subject treating of deletion burst and anesthesia general,

The exclusion criteria for the first selection phase based on qualifications and summary were non-response to the inclusion criteria and the absence of summary available.

2.2.3. Procedure of the Study and Extractions Data

After pooling the publications included or excluded by title and summary, THE studies have summer read in their entirety of manner independent.

Data was extracted using a data extraction grid (Appendix 3) developed from the *Cochrane* and PRISMA-P repositories.

This second stage has permit there selection definitive of the items in Following the same methodology as in the first step. We have could formalize THE points analyzes following:

- 1) title,
- 2) author
- 3) review,
- 4) population of the study (kind actor, country, number of topics),
- 5) year of the study (Or by default, year of publication),
- 6) objective main of the study,
- 7) methodology used,

2.2.4. Analyse of There Quality of Studies

The level of quality of each study was assessed using different scales: the COREQ guidelines [12] for qualitative research, the criteria STROBE [13] for descriptive studies, the ENTREQ criteria [14] for qualitative research syntheses (Appendix) and the PRISMA-P criteria [9] for the journals of literature.

3. Results

HAS. DESCRIPTION OF THE SELECTED STUDIES

Search equations and keywords used in the different databases data made it possible to reference 239 publications. After analysis 113 documents have been retained by consensus.

The elements retained were distributed as follows: 55 articles and 58 academic documents (thesis or memory) obtained from the research equations.

Table 1. The results of the research articles.

Article listed	number
Excluded on title And summary	n= 22
Duplicates Let's triple	not/ = 63
Items retained on title And summary	not = 113
Excluded After complete analysis	not = 41

4. Discussion

This literature review aimed to highlight the mechanisms neurophysiological of there burst deletion at course anesthesia general,

After their review of their literature two hypotheses were issued:

First of all the hypothesis of hyperexcitability cortical and second the hypothesis metabolic.

The hypothesis of hyperexcitability cortical

In This study reports the author's reports existence of a state hyperexcitability somatosensory cortical at course of an anesthesia deep generally associated has an EEG pattern of Bust removal.

This observation raises many questions related to the management of patients reaching this state to their following anesthesia- coma artificial.

Despite the fact that other comas of different etiologies (for example, various encephalopathies) share patterns of Bust suppression similar to those presented In this study, suggesting the involvement of ways of generation common, further investigations are necessary to determine if these guys of coma display the same hypersensitivity.

The answers in gust could be mentioned by a variety of stimuli (hearing, visuals and somatosensory). Here the authors have choose of put emphasis, on a type of stimulus that was clearly, both in amplitude and in duration, below the threshold.

The stimulus has summer transmitted at skull has through the bars ear of frame stereotaxic. Although poorly defined, the nature of these stimuli contains several benefits.

All First of all, in so much that stimulation mechanical, She East amplitude extremely scaled down because She born product not there loss of impalement intracellular (cells of diameter $\sim 10 \mu\text{m}$).

Second, the duration of the stimulus is extremely confined in time (250 μs), which gives the advantage of a precise triggering moment and stop overlapping effects on off in there answer.

The fact that burst responses can be evoked during the BS is not completely new [14]. Used stimuli vibration (duration 3 s) applied has there hand of patients below anesthesia has isoflurane. They caused burst suppression of EEG with a latency of approximately 0.5 s who were associated has an increase in frequency cardiac and had different characteristics from spontaneous bursts. They concluded that their puffs mentioned depended of the reactions autonomous triggered by THE stimulus. Contrary to have this study, of the results emphasize the absence involvement of the autonomic nervous system because no variation in frequency associated heart rate was recorded in response to stimulation. In addition, thrusts have summer mentioned below miscellaneous anesthetics, some being vasodilators isoflurane and others vasoconstrictors barbiturates suggesting that at least vasomotion has not influence the generation of puffs [15, 16].

In a recent study devoted to the mechanisms of slow

oscillations of the sleep, there slice thalamocortical in vitro its proven able of produce of the states Up And Down alternate spontaneously [17].

Of do of their nature basically disconnected of this preparation, her activity closely resembles that of the Burst suppression patterns mentioned in the comatose brain following deafferentation [18-20].

Thus, burst suppression aroused in this study could very well be essentially similar in nature to those of the study mentioned above. However, the authors emphasize that, during various behavioral states, the So-called "Up" states can reflect distinct realities and result from mechanisms different.

Additionally, bursts during Burst Suppression are different from burst suppression periods. Depolarization (Up states) of the slow-wave sleep oscillation because, unlike first, these latest born cannot be induced by there microstimulation.

Thus, the authors have established the presence of a relatively narrow state window associated At Burst deletion at course of which there stimulation somatosensory causes of the startles in the brain.

In out of this state (has of the levels anesthesia more superficial Or more deep), no obvious response could be detected, which does not mean that the brain does not respond, but rather that micro stimuli of the type used in this study did not could to provoke of answers.

That confirmed in besides the affirmation according to which the state of B.S. East A state Hyperexcitability. The appearance of this status window is prefigured by an increase progressive of the concentrations extracellular of Ca^{2+} Who can, on the one hand, transiently improve synaptic processes cortical, and, on the other hand, reduce the spontaneous discharge of neurons thanks to a best screening of the canals Na^{+} contributing Thus has there gradual appearance of suppression episodes [21].

In addition, the fact that the overall Ca^{2+} trend rather followed the levels isoflurane that the state Burst deletion himself suggests that others phenomena, requiring additional investigations, are at work in there modulation excitability of cortical network.

The refractory nature of the puffs was most likely linked to depletion phasic increase in extracellular Ca^{2+} and could be explained by the phasic drop in efficiency synaptic.

So, the character refractory would result of a process of disfacilitation, similar to that described in the case of the slow oscillation ($<1 \text{ Hz}$) of sleep at slow waves [22].

Burst activity is accompanied by an activity synaptic neuronal, in particular of NMDA, and action potential discharges also present data), which in turn would increase the influx of Ca^{2+} into THE cells [23].

Whether this input occurs at the presynaptic or postsynaptic level is difficult has determine in vivo. However, a series of studies suggest there preponderance of postsynaptic uptake [24-26].

If this is also the case during the BS, this would imply that the cessation of the activity of bursting results from the progressive drop in synaptic transmission during phase of

burst.

Once neuronal activity has ceased, ATP pumps can restore extracellular Ca^{2+} concentration to control values. The dynamics of return of extracellular Ca^{2+} to control levels, if it is the same order of greatness with their duration of there period refractory, would support the idea that there generation of a new startle is not possible that after that efficiency synaptic crossed A threshold.

The neuroprotective characteristics of all anesthetic agents used are based, among other things, on a dose-dependent reduction in metabolic rate cerebral [15].

It is therefore prudent to consider that ATP reserves should not be affected during there B.S. And are little susceptible of play A role in influencing there duration the period refractory.

This appearance need However a verification additional. The intragial recordings reveal for the first time both aspects following.

First of all, the activity bursting East associated has of the potential of depolarization phasic, as foreseen account tenuous of the activity neuronal intense displayed during the gusts.

As the glial membrane potential is closely linked to the concentration extracellular of K^+ this depolarization reflects probably increase of K^+ extracellular.

Secondly, there progression of their depth of anesthesia has leave of diagrams of kind sleep towards a line isoelectric was associated has a depolarization keep on going off potential of there membrane glial of approximately 3 mV. This depolarization translated, according to the equation of Nernst, an increase of approximately 0.5 mm of their concentration extracellular in K^+ . [27-31].

In assuming that there concentration intracellular in K^+ gets up has 125 mm and taking into account a membrane potential of -90 mV, we obtain an extracellular variation in K^+ of 4 to 4.5 mm. The latter value corresponds to the point at which overall neuronal excitability changes from one excitability facilitated has an excitability altered [32, 33].

The bursting himself has summer considerably reduced in duration and in amplitude by blocking NMDA receptors, despite the fact that the burst occurred at fairly hyperpolarized membrane potentials. This apparent incongruity could explain by their location remote of the receptors NMDA by relation to the somatic site in which the presumed impalement of our neurons. Indeed, NMDA receptors are only found at low densities on THE membranes plasma extrasynaptic of the somata, of the stems dendritic and spines and never in post-membrane specializations synaptic to terminals GABAergic [34].

As noted previously, the B.S. East characterized by a wide synchronization activities neuronal [35].

The substrate of this synchronization has always summer supposed to rest on there transmission neuronal, and abolition responses mentioned by TTX brought A support additional has this affirmation.

It should be noted that a similar effect was achieved by closing the junctions incomplete, probably in the syncytium glial, This Who opens there discussion of the involvement of

glial cells in the propagation of activity bursting.

He has summer demonstrated that the network glial underlies the buffer spatial of K^+ [36] and this seems to be at work during various brain states, such as that the sleep and the epileptic discharges [37].

However, at this stage entrusting the glial syncytium with the responsibility of propagating the activity bursting during the B.S. could be hasty because, of a go, the CBX is a broad-spectrum gap junction blocker [38], and, else go, he blocked the activity of network of neurons in culture not involving not of junctions incomplete [39].

Thus, its systemic application could have shifted the general state of the brain into out of there window hyperexcitability. This appearance need an investigation complementary. There new discovery hyperexcitability at course of B.S. encourages has goodbye two aspects essential.

The origin of the puffs "spontaneous" and the impact of all stimulation somatosensory on comatose patients. The spontaneity of the gusts was generally supposed in all the studies previous on B.S. [1, 2] Some of them dealt with the pseudo-rhythmicity of bursts others of their appearance in differenced preparations [40, 41]. In view of these data, it could be that many gusts, Otherwise all, be the result of stimuli subliminals No detected. These Stimuli can be external as well as internal in nature. The fact that the brain pulsations appearing in the bloodstream were incapable to provoke burst responses, however, argues against the possibility that pure mechanical shocks in the parenchyma generate such responses in gust. This rather favors a sequence of relays conveying information sensory from the periphery to the brain. The variability of inter-intervals gusts would result In This case of there combination of there synchronization of the stimuli and from the moment of there period refractory to which these stimuli arrive.

The second aspect concerns the capacity of a deeply anesthetized brain or comatose to perceive signals from the outside world. Current data underline the fact that subliminal stimuli, imperceptible to a brain conscious, cause persistent and complex responses during SB. They will probably not leave memory traces in the brain due to properties amnesiacs known of anesthesia but could play a role in the maintenance of a rudiment of activity cellular, similar has the effect presumed of some sleep oscillations in the modulation of plasticity [42-44]. This could prove to be of utmost importance for the management of comatose patients and for post-comatose recovery.

The hypothesis metabolic

Another theory important East the hypothesis metabolic. Has ugly of a mathematical model, the authors showed how burst suppression occurs produced by the interaction between neuronal dynamics and brain metabolism [4].

In This Model neuronal-metabolic for there Burst deletion.

Here the authors developed a burst suppression model that combines of the effects at level of circuit local with of the effects more wide on the metabolism neuronal. In the model, the link between these two levels of physiology pass by the channel potassium addicted of ATP, Who East known for be

Express In the cortex and structures subcortical [45].

Activation of this channel serves to stabilize cell membranes, leading to alternating periods of activity and suppression lasting several seconds. We know that altered neurometabolic dynamics can occur in each of the conditions associated with suppression of puffs: in general anesthesia, by a reduction in neuronal activity and subsequent reductions in CMRO [46, 47]; In the lesions hypoxic/ischemic, by of the discounts aberrant metabolic regulation due to diffuse lesions or by a stress oxidative direct [48, 49]; in case hypothermia, by of the discounts direct of rate metabolic [50, 51]; And In encephalopathy developmental, by A dysfunction neuronal And metabolic [52].

Involve the metabolism cerebral in the mechanisms neuronal of deletion of the gusts establishes A link physiological unifying between the main etiologies of phenomenon.

The model provides an explanation of the features power states of there deletion of the gusts:

- 1) the gradual and continuous increase in burst suppression with deeper inactivation levels is due to a gradual reduction metabolism, by example by a decrease in there CMRO;
- 2) there synchrony space of the appearance And of gap of there gust can Occur has through there wide demonstration of these changes metabolic processes, including in subcortical structures (noting that the model current East spatially compact); and
- 3) recovery of rhythms in bursts is due to recovery basal dynamics at the level of the neuronal circuit caused by transient increases of energetics.

Of more, the model suggests of news features phenomenological:

- 4) a derivative of the activity rhythmic At course of a salvo in reason of a slow exhaustion and of an increase subsequent of and
- 5) A limitation of high-frequency intra-burst activity independent of the strength of inhibition synaptic.

Consistency with the studies previous ones.

The model is consistent with descriptions of burst suppression in anesthesia general, of the lesions cerebral hypoxic-ischemic and of encephalopathy infantile [53].

At the cellular level, the model is consistent with [54], which showed broad burst synchronization and strong correlation between cortical peak And the activity of the gusts, measured by the potential of field. The do that some cells subcortical produce of the peaks during there quiescence cortical may be due to differential expression of the K ATP channel in these structures. It was shown in ref. that burst activity is correlated with a decrease of calcium extracellular [55].

As suggested in there exhaustion of calcium extracellular would prohibit synaptic transmission, leading to alternating periods of startle and quiescence. Such a mechanism does not immediately take into account characteristics such as the quasi-periodicity of bursts or changes continuous BSR, nor does it provide a transparent link with the range deletion

etiologies of the gusts.

Nevertheless, a regulation calcium aberrant can certainly to accompany the mechanisms suggested in our model. Indeed, a brain metabolism and a production of ATP compromise can to alter the pumps neuronal homeostatic for the maintenance of the levels of calcium, catchy their exhaustion during a burst. The suppression of neuronal discharge via the opening of the channel K ATP maximizes energy available for restoration calcium.

In ref. 11, the authors also show that after the appearance of a burst, it there is a refractory period during which neuronal activity cannot be induced by a microphone stimulation external [56].

This result is again consistent with our model, in which the K channel ATP remains open after the peak stops (due to the time constant of the variable trigger in there ref. [57]

Thus, the excitability of neurons is severely reduced during the period immediately following the offset of the burst. As ATP recovers, it gradually becomes easier to initiate a burst, which can correspond to increased excitability [11] and higher variance of the duration of there salvo. Let us note in besides that there relationship between metabolism and physiological oscillations have been well studied at the level of mitochondria and there cardiac dynamics [58].

In this context, models have been developed which suggest how the Oxidative stress can lead to slow, high amplitude oscillations and an arrhythmia through mechanisms involving membrane channels dependent of ATP [59].

Such mechanisms are similar to those in our model for suppression gusts. Model predictions. The model predicts the manifestation of suppression of bursts in scenarios involving brain metabolism seriously compromised. The practice of induced hypothermia during cardiac surgeries provides a powerful, parametric way to test this mechanism [4].

5. Conclusion

Studies have not yet precisely determined the mechanism behind the burst suppression, although many have used animal models, human data and mathematical models to better understand the underlying neurophysiology. The cortical hypersensitivity hypothesis. Help of a model of cat Or he exist an answer neuronal has there stimulation during there Burst suppression.

Hyperexcitability would come from of a concentration increased of calcium extracellular resulting of doses high isoflurane. The suppression of the burst could then be explained by a refractory period post-burst where the mechanical stimulus depends on the time between the end of a burst and the next stimulus.

The metabolic hypothesis Using a mathematical model, the authors showed how burst suppression occurs through the interaction between there dynamic neuronal and the cerebral metabolism.

In this model, a decrease in cerebral metabolic rate, associated with a stabilization by adenosine triphosphate-

gated potassium channels (ATP), leads to burst suppression. According to this review burst suppression need a study prospective goods in-depth for goods statement the mechanisms imply for improved care of patients in resuscitation.

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