Hypothesis for Propofol-induced Burst-Suppression: systemic vascular action or cortical disconnection?


Abstract:
The pathophysiology of the burst-suppression (BS) EEG pattern induced by propofol remains debated. We performed on-line EEG recording in both hemispheres, before and after cortical isolation, during 3 operations of functional hemispherectomy. After isolation of one hemisphere, we studied the participation of the vascular propofolium induced electrical activity. The lesioned tissue showed a more rapidly appearing pattern of BS. We concluded that the mechanism of action of propofol induced cortical b-s pattern in chronic lesions is a result of several actions, firstly the state of the cortical tissue, secondly the disconnection of ascending thalamo-cortical pathways as a direct cortico-cortical level of modulation.

Introduction:
The electroencephalographic (EEG) burst-suppression (BS) consists of an alternation between transient sequences of high voltage slow waves possibly intermingled with sharp waves, and periods of depressed background activity or complete EEG flatness. It can be observed normally in sleep, after pharmacologically-induced coma (e.g. propofol or methohexital). Propofol is used both to induce anaesthesia and to treat status epilepticus. Its administration may result in an EEG image of BS, the pathophysiology of which remains largely unknown.

Because it was also observed spontaneously during various interventions isolating the cortex (functional lobectomy or leucotomy). Steriade concluded that BS could result from a disconnection of the cortical networks from their pre-thalamic and thalamo-cortical afferents. But it was also observed that BS recorded in isolated cortical areas could be modified by systemic administration of anaesthetic agents (e.g. propofol or methohexital).

This led Wernbom to conclude that BS was modulated at a cortical level and that its severity over isolated cortex blocks actually indicated the degree of persistent cortical-cortical connectivity in this block. In other words, two factors are likely to determine BS recorded over a cortical area: its degree of disconnection from sub-cortical influences, and its intrinsic pattern of cortico-cortical connectivity.

Functional hemispherectomy (FH) is indicated in severe refractory epilepsies (e.g. Rasmussen encephalitis, Sturge-Weber disease, porencephaly) (Villemure) and can be considered as a human model of complete cortical isolation (Villemure, Shelag). Indeed, it consists of a resection of the central region, combined with the disconnection of the frontal and parieto-occipital lobes, which are left in place, from their thalamo-cortical and basal-ganglio-cortical connections. That is, FH allows to obtain recordings from frontal and parietal-occipital lobes that are free from all ascending (or reverberating) subcortical influence, but in whom the cortico-cortical connectivity is left intact.

We studied propofol-induced BS simultaneously in both hemispheres (electrocorticogram on the lesioned side, scalp EEG controlateral), before and after BF. Our hypothesis was that hemispherectomy would influence the dynamics of BS induction by propofol. That is, this model would enable us to study the influence of the disconnection of sub-cortical ascending pathways and pharmacological influences on the cortico-cortical connectivity.

Results:
Before FH (Cases 1,2,3)
Propofol gave rise to a symmetrical appearance of BS only in Case 1. In Case 2, BS appeared earlier in the lesioned hemisphere. Case 3 initially disclosed a low-voltage monotonous signal from the atrophic hemisphere (2 sec earlier in the contralateral hemisphere) followed by recovery of a symmetrical BS.

Before functional hemispherectomy
In Cases 1 and 2, the BS appeared earlier the lesioned hemisphere but increasing doses of propofol gave rise to a symmetrical flattening in both hemispheres. There was a clear bolus effect. Interestingly, the BS that reappeared after the bolus effect was symmetrical (Cases 1 and 2). In case 2 after FH there was a BS pattern in the ipsilateral lesioned hemisphere (without propofol induction). There was also a propofol threshold effect, whose level seemed to be different in each case. At low dose, BS appeared earlier in the lesioned hemisphere, but, at higher doses, the effect was symmetrical.

The controlateral EEG monitoring showed disappearance of the frontal-temporal epileptic focus after frontal lobectomy in Case 1. In Case 2, no epileptic discharges were observed in the controlateral hemisphere throughout the operation. In Case 3, the controlateral EEG disclosed repetitive epileptic discharges, which were not modified during the intervention.

After functional hemispherectomy
In Cases 1 and 2, the BS reappeared earlier the lesioned hemisphere but increasing doses of propofol gave rise to a symmetrical flattening in both hemispheres. There was a clear bolus effect. Interestingly, the BS that reappeared after the bolus effect was symmetrical (Cases 1 and 2). In case 2 after FH there was a BS pattern in the ipsilateral lesioned hemisphere (without propofol induction). There was also a propofol threshold effect, whose level seemed to be different in each case. At low dose, BS appeared earlier in the lesioned hemisphere, but, at higher doses, the effect was symmetrical.

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Discussion:
This study of ECoG with controlateral scalp EEG gave an opportunity to study the propofol-induced modifications of cortical electrogenesis, before and after FH, using the controlateral hemisphere as a control throughout the procedure. It must be pointed out that, inevitably, the positions of the ECoG electrodes were slightly modified after FH due to tissue removal. FH is an interesting human model of cortical isolation, which may shed light on the physiology of the BS induction by propofol. Indeed, propofol can induce BS either by influencing pre-thalamic or thalamo-cortical afferents, in which case its influence must be different before and after FH, or by direct action on the local cortico-cortical networks, in which case the influence of FH could be less dramatic.

The observation actually showed quite different patterns in the 3 patients. Case 3 presented a severe hemisrophy of undetermined origin with probable bilateral lesions (Sturge-Weber disease). This can explain the poor signal obtained on the involved side and the epileptic abnormalities in the controlateral hemisphere, which remained unchanged after the operation.

Both Cases 1 and 2 presented a left lesion perinatal vascular lesion. In Case 1, propofol induced a symmetrical BS before FH, and an asymmetrical pattern, appearing earlier in the lesioned hemisphere, after FH. In Case 2, although propofol already gave rise to an asymmetrical pattern pre-operatively, with earlier BS appearance on the lesioned side, the asymmetry was enhanced after FH. However the BS was already present in the lesioned hemisphere after FH before administration of propofol. At higher doses, the alterations were symmetrical.

All these data argue in favour of an influence of the cortical-subcortical disconnexion induced by FH, in addition to the fact that the same overall pattern was present before and after FH argues in favor of possible systematic influence of propofol on local cortical networks, with a possible higher sensitivity of lesioned tissue. If this is true, the fact that, in Case 2 the BS pattern was already asymmetrical before FH and remained so after FH would imply the presence of a more extensive chronic lesion, as well as the image of FH prior FH the lesioned isolated hemisphere, when compared to Case 1.

Earlier reports (Henry, Steriade) have documented epileptogenic cortical activity with spontaneously appearing by afferents from cortex to leucotomy or lobotomy procedures, confirmed in one of our cases (case 2). This was proposed to be a result of a disconnexion of thalamo-cortical circuitry.

Conclusion
We suggest that at least 3 factors could influence BS appearance after propofol administration: (1) a systemic action on local cortical networks (2) with a possibly higher sensitivity of lesioned tissues, and (3) a probable influence of cortical disconnection from ascending thalamo-cortical influences.

Materials and methods:
Recordings of the ipsilateral electrocorticogram (ECoG) and controlateral scalp EEG were obtained under light general anaesthesia (sevoflurane si possible, propofol les doses). Propofol was first administered at standardized doses (0.8, 2.8, 3.0 and 7.2 mg/kg) before FH. The regulation time was 10 to 30 minutes. BS was defined as alternations between 1-6 sec bursts of mixed medium-high amplitude slow activity and low-to-medium amplitude fast activity, and 1-3 sec spikes of electrocerebral suppression. The degree of suppression during suppressive epochs was rated mild (low to medium amplitude), moderate (non-sustained low amplitude), or severe (flattening (absence of any discernible electrogenesis) (Wernbom). The following parameters were considered: BS appearance, inter-hemispheric symmetry/asymmetry, BS disappearance. The same procedure was repeated after total isolation of the hemisphere (FH).