Occurrence of and risk factors for electroencephalogram burst suppression during propofol–remifentanil anaesthesia

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**Editor’s key points**

- Burst suppression (BS) from the EEG occurs during deep anaesthesia, but also in cases of metabolic or haemodynamic brain injury.
- This study retrospectively studied the occurrence of BS during bispectral index-controlled propofol and remifentanil anaesthesia.
- BS is mainly observed in elderly male patients or in patients with a history of coronary artery disease.
- The mechanisms underlying BS and the potential consequences for the patient’s postoperative outcome remain unsolved.

**Background.** Suppression ratio (SR) derived from bispectral index (BIS) monitoring is correlated to EEG burst suppression. It may occur during deep anaesthesia, but also in the case of metabolic or haemodynamic brain injury. The goal of the study was to describe the occurrence of SR and to determine factors associated with SR during propofol–remifentanil general anaesthesia maintenance.

**Methods.** We conducted a post hoc analysis of BIS recordings in consecutive patients included in two multi-centre trials, undergoing non-cardiac surgery using a dual closed-loop BIS controller allowing automated propofol–remifentanil administration. The percentage of time spent with a BIS value between 40 and 60 (T_{BIS 40–60}) was measured. Two groups of patients were defined: the SR group, including patients with at least one episode of SR value >10% lasting more than 1 min, and the control group. Factors associated with SR were analysed using a stepwise multivariate analysis.

**Results.** A total of 1494 patients [age = 57 (17) yr; T_{BIS 40–60} = 76 (17%)] were analysed and 131 (8.7%) patients constituted the SR group. The main independent factors associated with SR were advanced age [odds ratio (95% confidence interval) = 4.80 (1.85–12.43) (P = 0.027), 10.59 (3.76–29.81) (P < 0.0001), for categories of age 60–80 and >80 yr, respectively], history of coronary artery disease (CAD) [2.53 (1.47–4.37) (P = 0.001)] and male gender [1.57 (1.03–2.40) (P = 0.03)].

**Conclusions.** The occurrence of SR during BIS-controlled propofol and remifentanil anaesthesia is mainly observed in elderly male patients or in patients with a history of CAD. The mechanisms underlying SR and the potential consequences for the patient’s postoperative outcome remain unsolved.

**Keywords:** anaesthetic techniques, i.v. infusion; monitoring, depth of anaesthesia; physiology, neurophysiology; potency, anaesthetic, age factors

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The algorithm behind the bispectral index (BIS) value incorporates three sub-parameters: the relative \( \beta \) ratio, derived from the power EEG spectrum; the SyncFastSlow, expressing relative synchrony of fast and slow waves derived from bispectral analysis; and a suppression ratio (SR) that quantifies the proportion of burst suppression (BS) EEG pattern or isoelectric activity.\(^1\)\(^2\) Several studies have reported a correlation between too deep anaesthesia and poor outcome after general anaesthesia. Monk and colleagues\(^3\) suggested that a cumulative deep hypnotic time, defined by a BIS value below 45, was an independent predictor of 1 yr mortality after major non-cardiac surgery. Three recent studies also strongly suggested an association between a cumulative duration of intraoperative low BIS value and postoperative mortality after cardiac\(^4\)\(^5\) or non-cardiac surgery.\(^5\)\(^6\) However, none of these studies reported the occurrence of SR.

The BS EEG pattern is characterized by alternating periods of normal to high voltage activity changing to low voltage or even isoelectricity rendering the EEG inactive in appearance.\(^7\)\(^8\) The burst SR is a time domain EEG parameter developed to quantify this phenomenon.\(^9\) To calculate this parameter, suppression is recognized as periods longer than 0.50 s during which the EEG voltage does not exceed approximately \( \pm 5.0 \text{ mV} \). The time in a suppressed state is measured, and the SR is reported as the fraction of the...
epoch length where the EEG is suppressed.\textsuperscript{9} Correlation between the SR derived from BIS analysis and the BIS surface EEG pattern during general anaesthesia has been reported.\textsuperscript{10} 11 SR is believed to be a strong, synchronized outflow of thalamic discharges to a widely unresponsive cortex.\textsuperscript{12} The proportion of isoelectric periods is higher with increasing anaesthetic drug concentrations, until eventually the EEG pattern becomes completely isoelectric.\textsuperscript{13} 14 This suggests that SR could be an indicator of too deep anaesthesia.\textsuperscript{1} 14 15 SR is also seen during coma or brain death but never during physiological sleep.\textsuperscript{16} Several case reports also suggest that SR could be associated with intraoperative metabolic disorders such as hypothermia,\textsuperscript{17} 18 hypoxia,\textsuperscript{19} hypoglycaemia or vascular brain injury,\textsuperscript{18} 20–22 and to brain death.\textsuperscript{23–26} However, little is known about the prevalence and risk factors associated with the occurrence of SR during BIS monitored anaesthesia.\textsuperscript{7} 22 27 The main goal of this study was to describe the onset, occurrence, and risk factors for SR during general propofol–remifentanil anaesthesia maintenance.

**Methods**

**Study design and BIS monitoring**

We conducted a post hoc analysis of two European multi-centre trials recording intraoperative BIS in 1494 patients undergoing elective surgery (intracranial excepted) under general anaesthesia. Adult patients with cerebral disease or with chronic use of psychotropic drugs, cardiac pacemaker patients and pregnant or breast-feeding women were not included. Patients (n=914) were included in the PosaAnes trial (registered with ClinicalTrials.gov, number NCT-00896714) and Boucle-N\textsubscript{2}O trial (n=580; NCT-00547209). For both trials, a dual closed-loop controller was used allowing the automated titration of propofol and remifentanil guided by the BIS. The controller measures and calculates the difference between the setpoint (BIS=50) and the measured BIS. If different from 0, the controller determines a new concentration of propofol, remifentanil or both using the pharmacokinetic model of Schnider and colleagues\textsuperscript{28} for propofol and the model of Minto and colleagues\textsuperscript{29} for remifentanil. The error size determines which drug will be modified: if the BIS error is small only the remifentanil is changed, if the BIS error is higher, the two drug concentrations are modified.\textsuperscript{2}

The PosaAnes trial was an observational study, designed to identify factors influencing anaesthetic drug requirements such as the time, type, and duration of surgery. We planned to recruit 4500 patients. The Boucle-N\textsubscript{2}O trial was a randomized controlled study designed to determine the sparing effect of 60% nitrous oxide on propofol and remifentanil requirements. This trial demonstrated that the sparing effect of nitrous oxide was limited to 6% for propofol. The occurrence of at least one episode of SR>10% was not significantly different between patients receiving nitrous oxide or not.\textsuperscript{2} In all patients, patient characteristic data, past medical history, and duration of surgery were recorded. Upon arrival in the operating theatre, a dedicated indwelling venous catheter was connected via a three-way SmartSite\textsuperscript{6} (Alaris Medical Systems, San Diego, CA, USA), with a priming volume 0.3 ml) to an infusion pump, and routine monitoring was started. The BIS electrode (Zipprep, Covidien, Mansfield, MA, USA) was positioned on the patient's forehead and connected to either an A-2000 XP (version 3.11) BIS monitor (Covidien) or a BIS Module (version 4.0 XP, GE-Healthcare, Helsinki, Finland). For all patients, anaesthesia was performed using a dual closed-loop controller allowing automated propofol–remifentanil titration guided by the BIS. A standard personal computer was used to provide a user interface and to control communication with the BIS monitor and with both propofol and remifentanil infusion pumps (Alaris Medical, Hampshire, UK) via an RS232 serial port (Infusion Toolbox 95\textsuperscript{26} version 4.11 software).\textsuperscript{30} Electrode impedance was checked and the BIS sampling rate was 256 Hz, with a 15 s smoothing rate. A valid BIS measurement was assumed when the signal quality index was >50.

**Statistical analysis**

Statistical analysis was performed in our Biostatistics Department using SAS 9.02 software (SAS Institute, Cary, NC, USA). Results are expressed as mean (SD), median (inter-quartile...
Results

Age distribution, duration of surgery, proportion of patients with a past medical history of coronary artery disease (CAD), and the average normalized dose of propofol of patients included in the PosoAnes and Boucle-N₂O trials differ only slightly (Table 1). Therefore, for the analysis, the data of the 1494 patients [age=57 (17) yr] could be aggregated. We recorded 3742 h of closed-loop anaesthesia during which 217 074 target modifications of propofol and remifentanil were made by the controller.

One hundred and thirty-one (8.7%) patients experienced at least one episode of SR values >10% for more than 1 min during maintenance of anaesthesia, and constituted the SR group. In these patients, a total of 257 episodes of SR were recorded. The percentages of patients in each SR category in the total number of patients and in the SR group are given in Figure 1.

The result of the univariate analysis comparing the SR and control groups is shown in Figure 2. Age, male gender, ASA physical status, past medical history of CAD, congestive heart failure or diabetes mellitus, \(T_{\text{BIS}}\) 40–60, intraoperative use of antihypertensive medication, and average doses of anesthetic were the variables included in the multivariate analysis. The main independent factors associated with occurrence of SR were advanced age, past medical history of CAD, and male gender (Table 3). The distribution of different age categories for the SR group is shown in Figure 2.

The analysis of the individual recordings focused on the period surrounding the occurrence of each episode of SR allowed us to individualize three distinct patterns (Fig. 3A–C and Table 4). Pattern A, observed in 118 (46%) cases, was characterized by the recording of at least one BIS value >60 in the 5 min period before SR occurrence (representative recording shown in Fig. 3A). In pattern B, observed in 90 cases (35%, Fig. 3C), BIS value was <40 at SR occurrence \(t_0\), and no BIS value >60 was reached in the 5 min period of recording before SR occurrence. In pattern C, observed in 49 (19%) cases, BIS values recorded in the 5 min period before occurrence and at onset \(t_0\) of SR value >10 were within the target range (Fig. 3A). The effect-site concentrations of propofol and remifentanil, calculated by the controller, and their changes in the 5 min period were compared between the three patterns using Tukey’s post hoc analysis and are given in Table 4. Finally, 118 or 0.5‰ target modifications by the closed-loop controller were followed by SR.

Discussion

The main finding of this study was that the occurrence of transient periods of BS or isoelectric activity, attested by the recording of SR value >10 for more than 1 min, was observed in 8.7% of patients undergoing different types of non-cardiac surgery during propofol–remifentanil anaesthesia. Main independent factors associated with SR were advanced age, past medical history of CAD, and male gender.

Ageing was an independent risk factor of SR, with an odds ratio >10 in patients over 80 yr of age. This may be related to the alteration in anaesthetic drug pharmacokinetic and pharmacodynamic responses in the elderly.28 29 Interestingly, age-related SR occurred, although the dual closed-loop controller that we used took into account the pharmacokinetic particularities of the older patients by using the models of Minto and colleagues29 31 and Schnider and colleagues28 32 in order to reduce the risk of drug overdosing. However, these two models were determined using a limited number of healthy volunteers in clinically controlled conditions and not in elderly patients suffering from several comorbidities. An alternative explanation of the age-related occurrence of SR is linked to the modification of skull conductivity induced by ageing.33 Elderly patients could have reduced skull conductivity that alters the EEG signal collection which could lead to a higher incidence of SR during anaesthesia. On the other hand, our results show that SR was less prevalent in women. Several studies have already shown sex-related differences in the pharmacodynamic effect of anaesthetic agents and support our findings.34 35

SR is a processed EEG marker of BS that is automatically computed and displayed during BIS monitoring.10 SR is an estimate of the suppressed EEG amount observed over the last minute. The instantaneous BIS value is a weighted, non-linear combination of core features, including the SR.8 The weight of the SR to calculate BIS is itself a function of SR. SR has no contribution to BIS for SR<10%, it has linearly increasing weight as it increases, and completely determines BIS when >50%.1 Using the 15 s smoothing rate, the EEG
used in calculating the current non-suppression component of BIS uses the last 15 s of artifact-free EEG available in the 1 min history buffer. So, if SR < 10% and assuming no artifact in the recent past, BIS provides an average picture of the patient state that is on average \( \approx 7.5 \) s old (i.e. half of the smoothing rate duration). If there is an artifact, then the average age of the data used is older because the algorithm has to look at older data to find artifact-free data to use. If there is more than 45 s of artifact in the last minute, then there are insufficient data to calculate a BIS index. If SR > 50% so that BIS is completely determined by SR, then the calculation window is roughly 1 min long. In the absence of artifact and using a 15 s smoothing rate, the average delay of EEG used in the BIS increases from 7.5 s for SR < 10 to 30 s for SR > 50. SR could easily be used intraoperatively by anaesthetists without technical expertise in EEG monitoring. However, intraoperative incidence of SR is poorly described, as in most trials studying depth of anaesthesia, analysis is centred on BIS rather than on SR values. Furthermore, its incidence may vary depending on the definition used. Thus, the impact of SR occurrence and of the duration of time spent with SR is unknown. In the current study, we chose to compare patients with and without at least one value of SR > 10% during more than 1 min, and we acknowledge that this choice may be considered as arbitrary. It was made: (i) to avoid the inclusion of patients with a very short period of SR, (ii) to limit the risk of including patients with a single value of SR due to artifacts, and (iii) because an SR value of > 10 is the lowest value of SR computed in the BIS index calculation.

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**Table 1** Patient characteristics and anaesthetic procedure. Data are mean (so), median (inter-quartile range). *Data are number (%). BIS, bispectral index; SR, suppression ratio. 

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=1494)</th>
<th>PosoAnes trial (n=914)</th>
<th>Boucle-N2O trial (n=580)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 yr</td>
<td>241 (16)</td>
<td>161 (18)</td>
<td>80 (14)</td>
<td>0.0006</td>
</tr>
<tr>
<td>40–59 yr</td>
<td>569 (38)</td>
<td>311 (34)</td>
<td>258 (45)</td>
<td></td>
</tr>
<tr>
<td>60–80 yr</td>
<td>571 (38)</td>
<td>366 (40)</td>
<td>205 (35)</td>
<td></td>
</tr>
<tr>
<td>&gt;80 yr</td>
<td>113 (8)</td>
<td>76 (8)</td>
<td>37 (6)</td>
<td></td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>767 (51)</td>
<td>468 (51)</td>
<td>299 (52)</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>ASA physical status III–IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>295 (20)</td>
<td>180 (20)</td>
<td>115 (20)</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Past medical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>91 (6)</td>
<td>42 (5)</td>
<td>49 (8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>58 (4)</td>
<td>31 (4)</td>
<td>27 (5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>90 (6)</td>
<td>57 (6)</td>
<td>33 (6)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypertension</td>
<td>405 (27)</td>
<td>240 (26)</td>
<td>165 (28)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>106 (7)</td>
<td>65 (7)</td>
<td>41 (7)</td>
<td>0.50</td>
</tr>
<tr>
<td>BMI &gt; 30 kg m(^{-2})</td>
<td>246 (16)</td>
<td>149 (16)</td>
<td>97 (17)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Duration of surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 h</td>
<td>711 (48)</td>
<td>470 (51)</td>
<td>241 (42)</td>
<td></td>
</tr>
<tr>
<td>2–4 h</td>
<td>559 (37)</td>
<td>325 (36)</td>
<td>234 (40)</td>
<td></td>
</tr>
<tr>
<td>&gt;4 h</td>
<td>224 (15)</td>
<td>119 (13)</td>
<td>105 (18)</td>
<td></td>
</tr>
<tr>
<td><strong>( T_{BIS&lt;40} )</strong></td>
<td>19 (17), 14 (8–25)</td>
<td>16 (16), 7 (12–21)</td>
<td>23 (17), 19 (11–30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>( T_{BIS 40 – 60} )</strong></td>
<td>76 (17), 80 (67–88)</td>
<td>78 (17), 82 (71–90)</td>
<td>73 (18), 77 (64–85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>( T_{BIS&gt;60} )</strong></td>
<td>5 (7), 3 (1–6)</td>
<td>6 (8), 4 (2–7)</td>
<td>4 (5), 3 (2–5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Remifentanil dose (( \mu g ) kg(^{-1}) min(^{-1}))</td>
<td>0.18 (0.08)</td>
<td>0.18 (0.08)</td>
<td>0.18 (0.08)</td>
<td>0.93</td>
</tr>
<tr>
<td>Propofol dose (mg kg(^{-1}) h(^{-1}))</td>
<td>5.0 (1.7)</td>
<td>5.2 (1.8)</td>
<td>4.7 (1.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SR group*</td>
<td>131 (9)</td>
<td>56 (6)</td>
<td>75 (13)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Fig 1** Percentage of patients in each SR category.
We found that SR > 10 was frequently associated with a deep level of anaesthesia attested by a BIS value of < 40 at the onset of SR (Table 4; patterns A and B). We found...
The fact that SR may have been favoured by the rapid deepening of anaesthesia induced by the closed-loop controller in the case of BIS value > 60 or a rapid BIS increase could be expected as these two factors are taken into consideration by the algorithm of the system, whereas it does not compute SR to adjust anaesthetic infusion rates. In some cases, SR occurred when BIS values in the 5 previous minutes were within the target range (pattern C), suggesting that the anaesthesia controller should not be considered as the sole mechanism of SR occurrence. Furthermore, during the 3742 h of BIS recording, more than 210 000 changes in effect-site concentration of propofol or remifentanil were made by the controller without SR occurrence. As such, other factors may be involved in SR occurrence in these cases, and several hypotheses can be raised. Hypovolaemia or changes in cardiac output have been shown to modify the pharmacokinetic–pharmacodynamic models of the anaesthetic drugs and may have favoured the occurrence of both deep anaesthesia and SR. On the other hand, haemodynamic impairment may induce a decrease in cerebral blood flow that may favour SR. In this regard, several case reports or short series have shown a relationship between SR and cerebral injury from various origins, including traumatic injury or hypoxaemia. Our study was not designed to address this issue, as intraoperative haemodynamic parameters or patient outcome was not recorded. SR monitoring could also identify periods of excessive anaesthesia, not detected by the calculation of the BIS value itself. One hypothesis is that propofol anaesthesia specifically induced spindle activity that does not exist during anaesthesia using volatile agents. The frequency of the spindles is usually in the range of 13–15 Hz, similar to alpha or beta activity ranges. These spindles could artifact the EEG activity, interpreted by the BIS monitor and
Nitrous oxide was used in patients in the Boucle-N2O trial. In two different prospective, multi-centre European trials. Study carries some limitations. Patients were primarily included fentanyl increases by three-fold the occurrence of SR when recently reported that manual control of propofol and remifentanil (Table 4 and Fig. 3c). A specific effect of such a concentration of remifentanil on either propofol concentration, recently reported by Yufune and colleagues, or on EEG signal, as suggested by other studies, could lead to SR without significant impact on the BIS value. However, interaction between the opioid and hypnotic was not specifically addressed in this study.

As this is a post hoc analysis of previous clinical trials, this study carries some limitations. Patients were primarily included in two different prospective, multi-centre European trials. Nitrous oxide was used in patients in the Boucle-N2O trial. BIS 40–60, BIS <40, or the occurrence of SR were similar between the two groups despite the use of nitrous oxide. We consider that we can aggregate patients included in these two trials since the same inclusion and exclusion criteria were used.

Another limitation is that we arbitrarily chose an SR threshold of 10%, although we do not know if such an SR value could be harmful. However, the effect of ageing on the presence of SR was unchanged whatever the SR threshold chosen. Anaesthesia was conducted using a dual closed-loop of propofol and remifentanil in all patients that permitted maintenance of anaesthesia in the target range in 76% of total anaesthetic time. The performance of the controller can be considered as adequate if compared with manual control of anaesthetic infusion by anaesthetists, reported in the literature, with a percentage of time spent in the target ranging from 49% to 77%. Moreover, we recently reported that manual control of propofol and remifentanil increases by three-fold the occurrence of SR when compared with the closed-loop control. On the other hand, these results might not be applicable to patients receiving volatile anaesthesia. We have not recorded the raw EEG, and thus cannot eliminate that the occurrence of SR was related to artefact, decrease in EEG total power in an ageing population, or spindles. Studies including simultaneously raw EEG, continuous arterial pressure, intra-cranial perfusion, and brain metabolism are necessary to determine the weight of these different parameters in SR genesis. Patient outcome was not recorded.

In conclusion, during BIS-controlled propofol and remifentanil anaesthesia, the occurrence of SR value 10 during more than 1 min is mainly observed in elderly male patients. The presence of SR could be an early sign of too deep anaesthesia. The question of the mechanisms of these periods of EEG B5 or isoelectric activity is unknown and can be related to haemodynamics, metabolism, or drug overdosing. The potential consequences for the patient’s postoperative outcome should be established in a prospective study.

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Conflict of interest

N.L. and T.C. are patent holders in France for the gain constants and the control algorithm (No. BFF80P669, Institut National de la Propriété Industrielle, France).

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