

## Correlation and agreement between bispectral index and state entropy of the electroencephalogram during propofol anaesthesia

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**Background.** Bispectral index (BIS) and state entropy (SE) monitor hypnosis. We evaluated the correlation and the agreement between those parameters during propofol anaesthesia and laryngoscopy with and without muscle relaxation.

**Methods.** A total of 25 patients were anaesthetized with propofol. At steady state (SS: BIS 40–50), they randomly received rocuronium (R) or saline (S); 3 min thereafter, a 20 s laryngoscopy was performed. Correlation (regression analysis) and agreement (Bland–Altman analysis) were evaluated before induction (baseline), at loss of eyelash reflex (LER), at SS and during the first 3 min after laryngoscopy (L).

**Results.** The correlation coefficient  $r$  (95% CI), the mean difference (MD) (95% CI), and the limits of agreement [lower-upper limits of 95% CI of MD (SD 1.96)] between BIS and SE were as follows. Overall recordings: 0.87 (0.83 to 0.90), 2.5 (1.2 to 3.0), and [–19.5 to 24.6]; Baseline: 0.45 (0.06 to 0.72), 7.6 (6.0 to 9.2), and [–2.7 to 17.9]; LER: 0.74 (0.47 to 0.88), 8.3 (3.5 to 13.2), and [–22.6 to 39.3]; SS, all patients: 0.41 (0.14 to 0.63), 2.0 (–0.5 to 4.6), and [–19.0 to 23.3]; SS, Group S: 0.36 (–0.07 to 0.68), 1.9 (–2.5 to 6.3), and [–25.0 to 28.8]; SS, Group R: 0.63 (0.32 to 0.82), 0.2 (–2.0 to 2.3), and [–14.0 to 14.4]; L, all patients: 0.49 (0.32 to 0.63), 0.7 (–1.6 to 3.0), and [–25.6 to 27.1]; L, Group S: 0.41 (0.13 to 0.63), 2.3 (–2.4 to 7.1), and [–36.7 to 41.3]; L, Group R: 0.72 (0.56 to 0.83), –0.6 (–2.2 to 1.0), and [–14.3 to 13.1]. The correlation was good except for SS in Group S. The MD was significantly different from 0 for overall recordings, during baseline and LER, but not for the other conditions. The agreement was poor except for baseline, and SS and L in Group R.

**Conclusions.** BIS and SE are globally well correlated. In contrast, agreement is poor as differences of more than 20 units are frequently observed, except for awake and paralysed patients.

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Depth of anaesthesia monitors which are currently available assess the hypnotic component of anaesthesia. Among them, the bispectral index™ (BIS) is commonly used to guide the administration of volatile and i.v. anaesthetics.<sup>1–3</sup> Spectral entropy of the EEG is another variable that has been introduced into clinical practice as an index of depth of anaesthesia.<sup>4</sup> It conceptually reflects the degree of complexity and irregularity of the EEG signal, and includes both the response entropy (RE) and the state entropy (SE). SE is computed over the EEG dominant frequency spectrum

(0.8–32 Hz) and is designed to monitor the depth of hypnosis. RE is computed over a larger frequency spectrum also covering the frontal EMG activity (0.8–47 Hz), and is designed to reflect the nociceptive–anti-nociceptive balance during general anaesthesia. As BIS and SE do perform well in monitoring one of the pharmacodynamic effects of anaesthetic agents, that is the hypnotic component of anaesthesia, the clinician could be tempted to use both techniques interchangeably. However, these techniques differ regarding their respective algorithm, scale and the delay

between EEG acquisition and screen values availability. One may therefore expect that BIS and SE do not agree in several circumstances.

Comparison of measurement techniques can rely on the calculation of their respective correlation coefficients or prediction probability values with pharmacokinetic or pharmacodynamic parameters. In that way, each technique is evaluated on its own behalf and its global performance is compared with that of others.<sup>5,6</sup> It is also possible to calculate the correlation coefficient between two methods. However, high correlation does not necessarily mean good agreement.<sup>7</sup> Agreement between two measurement techniques is best assessed by the analysis described by Bland and Altman,<sup>7</sup> which considers the difference between two methods against their mean.

The aim of this prospective blinded study was to assess correlation and agreement between BIS and SE during induction of anaesthesia using a propofol target-controlled infusion, during a steady-state level of hypnosis, and during nociceptive stimulation, either in the presence or in the absence of neuromuscular blocking agents.

## Methods

Following approval by the Regional Hospital Ethics Committee and informed consent, 25 adult (ASA status I or II) patients undergoing routine surgery under general anaesthesia were enrolled in this prospective blinded study.

### *Anaesthesia and monitoring*

Premedication consisted in alprazolam 0.5 mg and atropine 0.5 mg given orally 1 h before surgery. Upon arrival in the operating room, patients were equipped with a standard anaesthesia monitoring (Datex-Ohmeda™ S/5™, Helsinki, Finland). The BIS was monitored using the XP device (version 4.0) and a specific quatro sensor (Aspect Medical Systems, Newton, MA, USA and Leiden, The Netherlands). The EMG activity provided by the same monitor was also recorded (power in the frequency band 70–110 Hz, in dB). SE was monitored with the Datex-Ohmeda S/5 Entropy Module (M-Entropy™), using a specific entropy sensor (Datex-Ohmeda Division, Instrumentarium Corporation, Helsinki, Finland). The BIS sensor was appropriately applied on the left side of the forehead and the entropy sensor on the right side. Neuromuscular transmission was monitored by accelerography and assessed using the train of four (TOF) stimulation mode. In all patients, general anaesthesia was induced using a propofol target-controlled infusion (model of Marsh<sup>8</sup>) to achieve a BIS value between 40 and 50 defined as the steady-state (SS). Effect-site concentration of propofol was initially targeted at 2.5 µg ml<sup>-1</sup> and increased by steps of 0.5 µg ml<sup>-1</sup> after 4 min if necessary. During induction, all patients were managed by the same anaesthetist blinded to the study protocol, who continuously assessed the level of consciousness. After loss of the eyelash reflex (LER), patients were

ventilated with a face mask. Once SS conditions were achieved, the target concentration of propofol was not further changed and patients randomly received either 0.6 mg kg<sup>-1</sup> rocuronium (Group R; *n*=13), or the same volume of saline (Group S; *n*=12); 3 min thereafter, a 20 s laryngoscopy was applied. Randomization was performed using a computer-generated randomization list provided to the nurse in charge of preparing anaesthetic medications.

### *Data acquisition and analysis*

BIS, SE and EMG activity were continuously recorded using the Rugloop II® monitor (Demed, Temse, Belgium). Each variable was averaged over 1 min immediately after the following nine time points: before induction (Baseline), at LER, at SS, at rocuronium or saline injection (R/S), 2 min after (R/S+2), and 0, 1, 2 and 3 min after laryngoscopy (L). One patient from group S was excluded from the study because of unreliable entropy recording.

Correlation and agreement were assessed for the following conditions of recording, including *n* data pairs (number of patients×number of time points of recording) in each case: overall recordings (*n*=24×9=216), baseline (*n*=24), LER (*n*=24), SS in the absence of rocuronium [(SS in Group R)+(SS, R/S and R/S+2 in Group S), *n*=13+(11×3)=46], SS after rocuronium or saline (R/S and R/S+2 in Group R or in Group S, *n*=13×2=26 for Group R and *n*=11×2=22 for Group S), and during L for all patients (*n*=24×4=96), for patients of Group R (*n*=13×4=52) and for patients of Group S (*n*=11×4=44). Correlation between BIS and SE was assessed using classical least square linear regressions (LSRs). A sigmoid relationship between BIS and SE was also sought using LSR after logistic transformation of SE data for the entire set of recordings (*n*=216). Logistic transformation consisted in calculating  $\text{logit(SE)} = \text{LOG} [\text{SE}/(91 - \text{SE})]$ , where LOG=base 10 logarithm and 91=maximum possible value of SE. Agreement between the two indices was evaluated by a Bland–Altman analysis.<sup>7</sup> The 95% CI of the mean difference between BIS and SE served to test the null hypothesis that this difference was not significantly different from 0. The limits of agreement were defined as the lower limit of the 95% CI of the mean difference minus 1.96 SD and upper limit of the 95% CI of the mean difference plus 1.96 SD. The G-Power® software<sup>9</sup> served for power calculations.

Differences in EMG activity between and within Groups R and S were assessed using a two-way mixed-design ANOVA and Tuckey's HSD tests for post hoc comparisons. A *P*-value less than 0.05 was considered statistically significant. Normality of distribution was assessed when necessary.

## Results

Patients of Groups R and S were comparable in terms of age, weight, height and gender distribution as shown in Table 1.

## Regressions

For the overall recordings (Fig. 1), the correlation between BIS and SE was excellent ( $r=0.84$ , 95% CI 0.80–0.88), and an even better correlation was obtained using a sigmoid rather than a linear model ( $r=0.87$ , 95% CI 0.83–0.90). Although less strong, a significant correlation was also observed in all other conditions of recording, except for the SS condition in Group S ( $r=0.36$ , 95% CI  $-0.07$  to

0.68) (Table 2). The power of detecting a significant correlation between BIS and SE, assuming an  $r^2$  of 0.3, an  $\alpha$  threshold of 0.05 and a sample size of 22 (our lowest sample size) was higher than 0.8.

## Agreement analysis

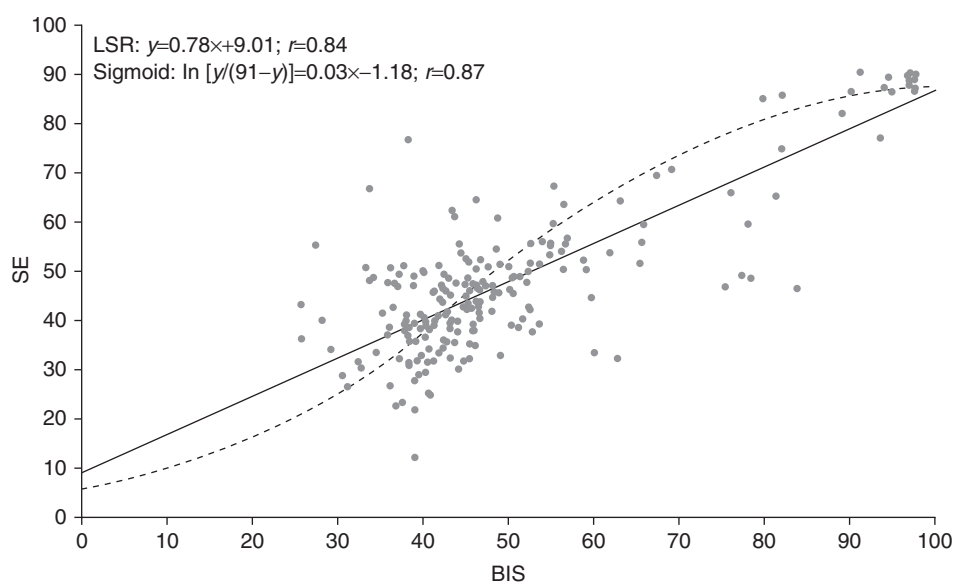
Mean difference between BIS and SE was significantly different from 0 for the overall recordings, at Baseline and at LER (Table 2), but not in the other recording conditions. The power of detecting a mean difference of 6, assuming a SD of the mean difference of 10, an  $\alpha$  threshold of 0.05 and a sample size of 22 was higher than 0.8. The limits of agreement for the overall recordings were  $-19.5$  to  $24.6$  (Fig. 2). The narrowest limits of agreement were observed at baseline ( $-2.7$  to  $17.9$ ) for the whole patient population, and at SS and during L (Fig. 3) in Group R ( $-14.0$  to  $14.4$  and  $-14.3$  to  $13.1$ , respectively). The worst agreement between BIS and SE was observed at LER ( $-22.6$  to  $39.3$ )

**Table 1** Patient characteristic data in Groups R and S. Results of statistical analysis are also provided. Data are means (SD) or counts. Student's  $t$ -tests were two-tailed and unpaired. Gender distribution was tested using a  $\chi^2$ -test with 1 d.f.

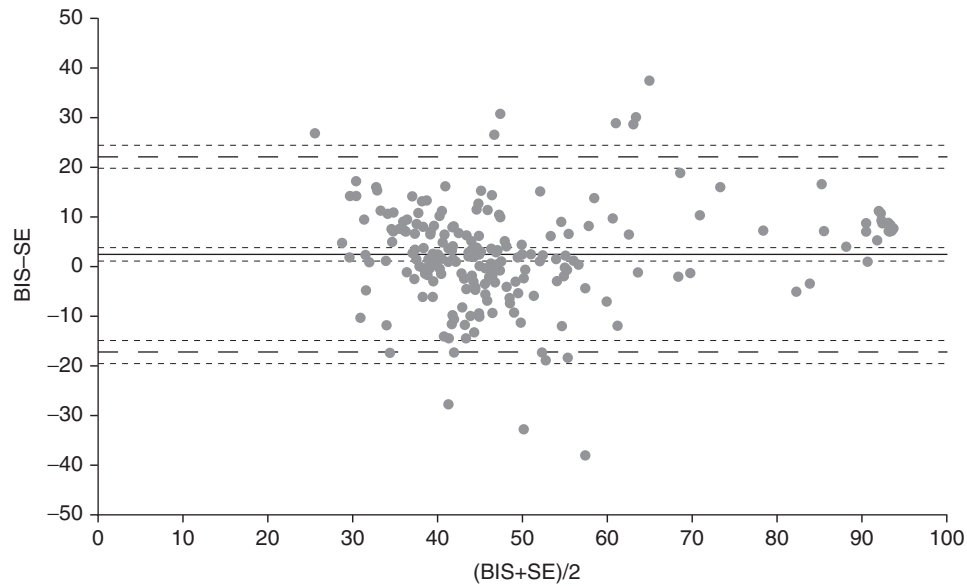
	Group R	Group S	Statistics
Age (yr)	43 (24–83)	46 (22–70)	$t_{(22)}=0.62$
Weight (kg)	68 (17)	74 (17)	$t_{(22)}=0.37$
Height (cm)	169 (9)	171 (11)	$t_{(22)}=0.56$
Gender (M/F)	6/7	6/5	$\chi^2_{(1)}=0.17$

**Table 2** Results of Bland–Altman analyses. The anaesthetic conditions were awake (baseline), loss of eyelash reflex (LER), steady state in patients of both groups (SS), steady state after rocuronium [SS (R)] or saline [SS (S)] injection, laryngoscopy in both groups (L), in Group R [L (R)] and in Group S [L (S)]. The mean difference between BIS and SE and its 95% CI, as well as the mean difference (SD 1.96) with 95% CIs are reported. The correlation coefficient  $r$  and its 95% CI obtained through classical least square linear regression between BIS and SE is provided for all conditions of recording. The last column provides the sample size in each situation ( $n$ ). See Methods for a detailed description of anaesthetic conditions of recording and sample size in each case

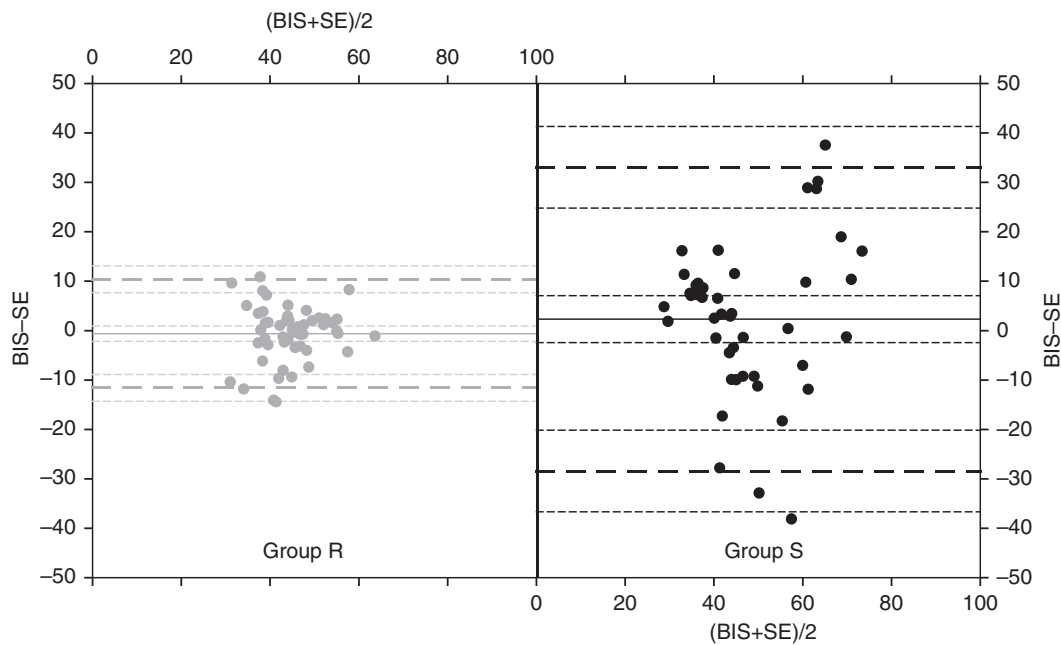
	$r$	Mean difference	Mean difference $-1.96$ SD	Mean difference $+1.96$ SD	$n$
Overall	0.84 (0.80–0.88)	2.5 (1.2–3.9)	$-17.1$ ( $-19.5$ to $-14.8$ )	$22.2$ ( $19.9$ – $24.6$ )	216
Baseline	0.45 (0.06–0.72)	7.6 (6.0–9.2)	$0.1$ ( $-2.7$ to $2.9$ )	$15.1$ ( $12.3$ – $17.9$ )	24
LER	0.74 (0.47–0.88)	8.3 (3.5–13.2)	$-14.2$ ( $-22.6$ to $-5.8$ )	$30.9$ ( $22.5$ – $39.3$ )	24
SS	0.41 (0.14–0.63)	2.0 ( $-0.5$ to $4.6$ )	$-14.8$ ( $-19.2$ to $-10.4$ )	$18.9$ ( $14.4$ – $23.3$ )	46
SS (R)	0.63 (0.32–0.82)	0.2 ( $-2.0$ to $2.3$ )	$-10.3$ ( $-14.0$ to $-6.6$ )	$10.6$ ( $6.9$ – $14.4$ )	26
SS (S)	0.36 ( $-0.07$ to $0.68$ )	1.9 ( $-2.5$ to $6.3$ )	$-17.4$ ( $-25.0$ to $-9.9$ )	$21.2$ ( $13.6$ – $28.8$ )	22
L	0.49 (0.32–0.63)	0.7 ( $-1.6$ to $3.0$ )	$-21.6$ ( $-25.6$ to $-17.6$ )	$23.1$ ( $19.1$ – $27.1$ )	96
L (R)	0.72 (0.56–0.83)	$-0.6$ ( $-2.2$ to $1.0$ )	$-11.6$ ( $-14.3$ to $-8.9$ )	$10.4$ ( $7.7$ – $13.1$ )	52
L (S)	0.41 (0.13–0.63)	2.3 ( $-2.4$ to $7.1$ )	$-28.4$ ( $-36.7$ to $-20.2$ )	$33.1$ ( $24.8$ – $41.3$ )	44



**Fig 1** One minute averaged SE values plotted against corresponding BIS values for the entire study period (grey circles). The linear (continuous) and the sigmoid (dashed) regression lines are also plotted. The equation corresponding to each line and the correlation coefficient  $r$  are provided.



**Fig 2** Difference between BIS and SE plotted against the mean between BIS and SE (Bland–Altman plot) for the entire study period (grey circles). The mean difference (continuous line) and its 95% CI (small dashed lines), as well as the mean difference (SD 1.96) (large dashed lines) with 95% CIs (small dashed lines) are also plotted.

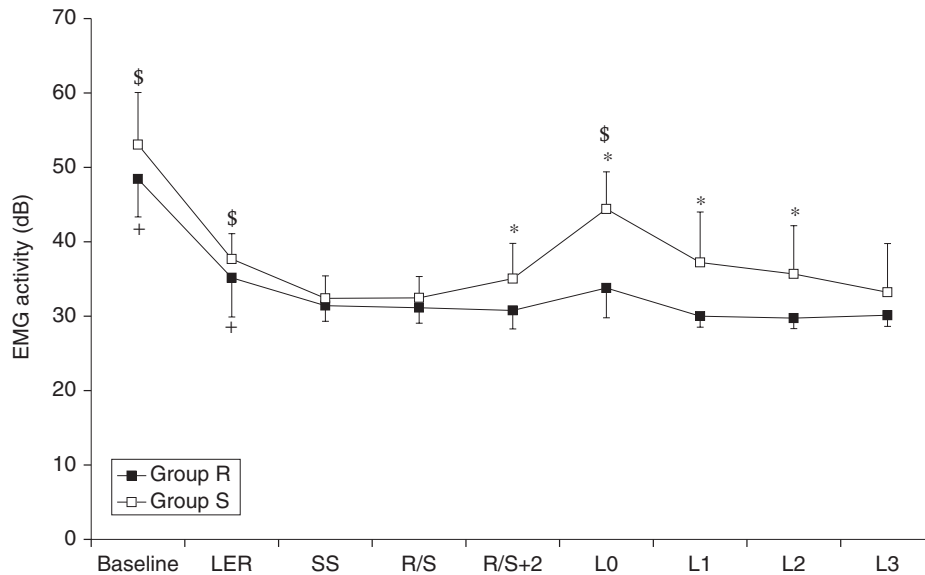


**Fig 3** Same as in Figure 2 but after laryngoscopy in Group R and Group S. Note that the limits of agreement in Group R are significantly narrower than in Group S.

for the whole patient population, and at SS and during L (Fig. 3) in Group S (–25.0 to 28.8 and –36.7 to 41.3, respectively). The limits of agreement between BIS and SE in Group R after laryngoscopy (–11.6 to 10.4) were inside the narrowest limits of the 95% CI of the mean difference (SD 1.96) in Group S during the same condition (–20.2 to 24.8), meaning that those limits of agreement were significantly narrower in Group R than in Group S during L.

#### *EMG activity*

As shown in Figure 4, induction of anaesthesia was associated with a decrease in EMG activity in both groups of patients. Two minutes after rocuronium administration, EMG activity was significantly lower in Group R than in Group S, and remained so until 2 min after laryngoscopy. Laryngoscopy induced a significant increase in EMG activity in Group S, but not in Group R. At the time of laryngoscopy, all but two patients of Group R had a TOF



**Fig 4** EMG activity profile in Group R (closed squares) and in Group S (open squares) during the conditions of recording (see text for complete description). \*=significantly higher in Group S than in Group R at R/S+2, L0, L1 and L2; +=in Group R, significantly higher at baseline than at any other point of recording and significantly higher at LER than at L1, L2 and L3; \$=in Group S, significantly higher at baseline than at any other point of recording, significantly higher at LER than at SS and R/S, and significantly higher at L0 than at LER, SS, R/S, R/S+2, L1, L2 and L3.

count equal to 0 and all patients of Group S had a TOF count of 4.

## Discussion

The main findings of this study are the following: (i) the overall correlation between BIS and SE was good; (ii) the agreement between the two parameters was globally poor; it may only be considered as good (limits of agreement in the range of 10 above or below the mean difference) in awake patients and in paralysed patients under SS hypnotic conditions, in the presence or in the absence of nociceptive stimulation; (iii) the mean difference in the range of 10 between BIS and SE noted at the awake state disappears during anaesthesia. Those results raise questions about the reasons for those discrepancies and their relevance in routine clinical practice.

A few studies only have looked at the relationship between BIS and SE. A recent report has emphasized that BIS and entropy changes according to modifications of the patient anaesthetic status may differ in time and amplitude.<sup>10</sup> In patients anaesthetized with sevoflurane, Ellerkmann have found a sigmoid relationship between entropy and BIS.<sup>11</sup> White and colleagues<sup>12</sup> have reported a good correlation between SE and BIS during induction ( $r=0.77$ ) and emergence ( $r=0.86$ ) from general anaesthesia with propofol and desflurane, which is consistent with the results of this study. However, good correlation does not necessarily imply good agreement. As stated by Bland and Altman, the correlation coefficient  $r$  measures the strength of a relationship between two variables, not the agreement between them. A perfect agreement absolutely requires

that all points obtained by plotting data pairs lie along the line of equality, while excellent correlation is obtained when the points lie along any straight line. In addition, a difference in scale of values between two parameters does not affect correlation but certainly does affect agreement. For those reasons, the Bland–Altman analysis appears to be the right statistical test to perform in an attempt to determine the degree of agreement between two measurement techniques.<sup>7</sup>

The only study that used the Bland–Altman analysis to compare BIS and SE has been published by Iannuzzi and colleagues<sup>13</sup> who investigated the relationship between BIS, SE and effect-site EC<sub>50</sub> for propofol at different clinical endpoints. They found a good comparability (mean difference 0.1) between the two parameters while the upper and lower limits of agreement were  $-19.9$  and  $19.6$ . The same type of analysis performed on data pairs averaged over 1 min over the entire period of our study yielded a mean difference of 2.5 and similar upper and lower limits of agreement ( $-19.5$  and  $24.6$ ). Obviously, the main difference between the results of the two studies lies in the fact that the mean difference is significantly different from 0 in this study. The reason for this may be related to differences in study design and in the way data were analysed. The patients in Iannuzzi's study were not premedicated while our patients received alprazolam 0.5 mg 1 h before surgery. The two studies differ regarding the temporal sequence of the propofol target infusion (Iannuzzi: initial target propofol concentration of  $1 \mu\text{g ml}^{-1}$  increased by  $1 \mu\text{g ml}^{-1}$  every 4 min, up to  $6 \mu\text{g ml}^{-1}$ ; This study: initial target propofol concentration of  $2.5 \mu\text{g ml}^{-1}$  increased by  $0.5 \mu\text{g ml}^{-1}$  every 4 min until obtaining the target BIS value). Patient's

status at the time of recording was also different: Iannuzzi and colleagues looked only at values recorded at loss of eyelash reflex and at loss of consciousness. In addition, we considered values recorded during baseline conditions, during a SS level of hypnosis and during nociceptive stimulation. Finally, we averaged our data over 1 min, while the team of Iannuzzi did not. By smoothing the recording, averaging data offer the advantage of getting rid of short delay time to time variability, and remove the effect of different sampling rates by the acquisition software. Nevertheless, the limits of agreement observed by Iannuzzi and those we observed in this study are large, as values of the indices may often differ by more than 20 units. Therefore, in clinical practice, using SE exactly the way BIS is used, with the same reference values, and expecting the same profiles of response to different events may not be appropriate.

A possible explanation for poor overall agreement between BIS and SE could be the difference in the delay between signal acquisition and the on screen display. Indeed, BIS values are classically considered to reflect events that occurred approximately 30 s before<sup>14</sup> while the time period required for processing entropy varies according to the EEG frequency, and is longer for lower frequencies such as those observed during an unconscious state.<sup>4</sup> However, smoothing the recording over 1 min, as we did, should normally attenuate this effect of time delay on agreement.

We further analysed the agreement between BIS and SE at different steps during the induction process. During the awake state (baseline), the mean difference between BIS and SE was significantly different from 0 and ranged between 6 and 9 units. This is not surprising as BIS values are scaled from 0 to 100 and SE values from 0 to 91. However, this difference disappeared at deeper stages of anaesthesia, even during nociceptive stimulation, and this can be asserted with a reasonable risk of type II statistical error. This observation is probably related to differences in the shape of the relationship between BIS or SE and depth of anaesthesia. Indeed, the relative contribution of several processed EEG parameters to BIS calculation varies as a function of anaesthetic depth.

Despite the mean difference in the range of 10, agreement between both measures was good in the awake patient, as the limits of agreement were  $-2.7$  to  $17.9$  around a mean difference of  $7.6$ . We also observed a significant difference in BIS–SE agreement after laryngoscopy between paralysed and non-paralysed patients [the limits of agreement between BIS and SE in Group R after laryngoscopy were inside the narrowest limits of the 95% CI of the mean difference (SD 1.96) in Group S during the same condition]. This finding was not confirmed in the absence of nociceptive stimulation, which could be related to a lack of statistical power. Therefore, we cannot conclude that the agreement between BIS and SE was better in paralysed than in non-paralysed patients during this specific condition of recording.

We can only conclude that agreement between BIS and SE was good in paralysed patients in the presence or in the absence of nociceptive stimulation, and that it was better in paralysed than in non-paralysed patients in the presence of nociceptive stimulation. A possible explanation could rely on the influence of EMG activity on BIS calculation, even when BIS is recorded using the XP device.<sup>15</sup> Figure 4 obviously shows that patients who received rocuronium had lower EMG activity than patients who did not during those periods of recording, and that laryngoscopy induced an increase in EMG activity in non-paralysed patients.

Finally, a possible limitation of this study is that we always recorded BIS and SE on the same side of the forehead, that is the left side for BIS and the right side for SE. It is noteworthy that it has been demonstrated that intra-individual differences may be observed when BIS is recorded at two different sites.<sup>16</sup> Therefore, we systematically chose the same site of recording in order to limit the effect of the site-related intra-individual variability of a given index. However, we cannot exclude that performing measurements always on the same side may have favoured poor agreement between BIS and SE.

In conclusion, we found an excellent global correlation between BIS and SE. BIS is higher than SE in the range of 10 units in awake patients and during induction of hypnosis. Agreement between BIS and SE was good in awake patients and in paralysed patients. In those conditions, clinicians may expect observing SE values similar to those that would have been observed with BIS, with a negative difference of approximately 10 units when the patient is awake. In contrast, agreement between both parameters was poor both globally and during the other conditions of recording, as differences of more than 20 units could frequently be observed. These discrepancies are partially explained by scale differences. They can also be related to site of recording, differences in calculation algorithms and delays as well as in shapes of the relationship between BIS, SE and the hypnotic level, and possibly to the effect of EMG activity on BIS calculation.

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