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Processed electroencephalography: impact of patient age and surgical position on intraoperative processed electroencephalogram monitoring of burst-suppression

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Abstract

We previously reported that processed EEG underestimated the amount of burst suppression compared to off-line visual analysis. We performed a follow-up study to evaluate the reasons for the discordance. Forty-five patients were monitored intraoperatively with processed EEG. A computer algorithm was used to convert the SedLine® (machine)-generated burst suppression ratio into a raw duration of burst suppression. The reference standard was a precise off-line measurement by two neurologists. We measured other potential variables that may affect machine accuracy such as age, surgery position, and EEG artifacts. Overall, the median duration of bust suppression for all study subjects was 15.4 min (Inter-quartile Range [IQR] = 1.0–20.1) for the machine vs. 16.1 min (IQR = 0.3–19.7) for the neurologists' assessment; the 95% limits of agreement fall within − 4.86 to 5.04 s for individual 30-s epochs. EEG artifacts did not affect the concordance between the two methods. For patients in prone surgical position, the machine estimates had significantly lower overall sensitivity (0.86 vs. 0.97; p = 0.038) and significantly wider limits of agreement ([− 4.24, 3.82] seconds vs. [− 1.36, 1.13] seconds, p = 0.001) than patients in supine position. Machine readings for younger patients (age < 65 years) had higher sensitivity (0.96 vs 0.92; p = 0.021) and specificity (0.99 vs 0.88; p = 0.007) for older patients. The duration of burst suppression estimated by the machine generally had good agreement

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Author contributions Study concept: DP, RZ, LA, JL Study supervision: JL Research data acquisition: DP, CT, DT, ST, Data analysis and interpretation: DP, SZ, LA, LZ, JL Supervised data analysis and interpretation: DT, MW Drafting of manuscript: DP, JL Revision of manuscript for intellectual content: SZ, LA, JL Correction of manuscript: SZ, LA, LZ, CT, DT, MW, ST, JL.

Conflict of interest Dr. Leung collaborates with Masimo Inc. on developing an algorithm in detecting adverse events. The research funding from Masimo was unrelated to this present project and manuscript submission.

Ethical approval Both relevant studies were approved by the University of California, San Francisco Human Research Protection Program (USCF HRPP). IRB Numbers: 13–12510 and 14–14273.

Consent to participate Informed consent was obtained from all forty-five study participants.

Consent for publication Manuscript contains no personally identifiable information.

compared with neurologists' estimation using a more precise off-line measurement. Factors that affected the concordance included patient age and position during surgery, but not EEG artifacts.

Keywords

Burst suppression; Electroencephalogram; Anesthesia; Processed EEG; Surgical position; Intraoperative neuromonitoring

1 Introduction

Burst suppression is a waveform pattern observed during electroencephalography (EEG) and indicates a profound impairment of neuronal metabolic rate and activity [1]. It is comprised of a "burst" component (low frequency, high amplitude [150–350 μV] waves) interspersed with suppression (flat < 25 μV isoelectric EEG activity) [1] (Fig. 1). Burst suppression patterns have been observed in hypothermia, hypoxia, drug overdose, coma, and patients undergoing general anesthesia [1, 2] and reflects a diminished basal level of brain activity. Recent evidence has suggested that intraoperative burst suppression during general anesthesia, as measured by processed EEG, is associated with a higher incidence of post-operative delirium [3-5]. We recently reported that preoperative cognitive impairment was associated with increased intraoperative EEG burst suppression, and that the effect of an intervention aimed at reducing burst suppression was more effective in those with preoperative cognitive impairment [6]. Therefore, there may be clinical utility to monitoring for burst suppression, particularly in those with cognitive impairment. In addition, accurately quantifying burst suppression is vital to understanding its impact on post-operative cognitive outcomes. Intraoperative EEG monitoring may serve as a valuable tool to guide the administration of anesthesia. However, there is evidence that current processed-EEG monitors lack adequate accuracy in estimating anesthetic depth during general anaesthesia [7] and estimating burst suppression [8].

One of the most widely used measurements for describing and quantifying burst suppression is the burst suppression ratio (BSR) [9]. BSR is a rolling average of the percentage of a preceding period (commonly a minute) that the EEG waveform was suppressed [9]. The majority of methods for automated burst suppression estimation involve a voltage threshold (often approximately ± 5 to ± 15 μV) along with a minimum amount of time that the EEG waveform must be within that voltage threshold (0.1 to 0.5 s) for a period of low voltage activity to be considered burst suppression [9].

There are several commercially available processed EEG monitors that incorporate a BSR: the SedLine® monitor, Bispectral Index (BIS) monitor, GE Datex-Ohmeda Entropy, Narcotrend Compact M, and SNAPII [10, 11]. For this study, we used the SedLine® monitor (Masimo, Inc, Irvine, CA), as it is the monitor that is primarily utilized at our institution.

Our recently published work investigated the accuracy of burst suppression measured by processed EEG using the SedLine® to predict post-operative delirium compared to off-line visual inspection by neurologists [8]. In this prior study, two neurologists visually assessed each 30-s epoch and assigned a duration of either 0, 10, or 20 s of burst suppression, rounding down to the lower limit of each designation. Each epoch was compared with the burst suppression duration as output by the SedLine®. The results demonstrated that the BSR underestimated the total duration of burst suppression compared to off-line visual analysis [8]. However, the reasons contributing to the discrepancy between SedLine® (machine)-generated BSR *vs.* off-line visual measurement of burst suppression were unclear.

Accordingly, this study's primary aim was to compare the accuracy of BSR in detecting the duration of burst suppression compared with off-line visual analysis using a more detailed approach. The secondary aim was to investigate potential reasons for the discrepancy between the two methods of analysis.

2 Materials and methods

2.1 Patient data

The sample of patient data included in this analysis were obtained from two related studies, one a prospective, observational study that occurred between May to December 2014 [8] and the other a randomized controlled trial that occurred from June 2015 to September 2017 [6]. For both studies, the inclusion criteria consisted of adult patients (40 years of age or older; or 65 years of age or older respectively), undergoing major, elective, non-cardiac surgery requiring general anesthesia, and an expected hospital stay of at least three days. The SedLine® Legacy Monitor was used to provide continuous processed EEG for all patients. Exclusion criteria included patients who did not understand the study, non-English speaking patients, and patients not undergoing general anesthesia. The institutional human research committee approved both studies, and all study patients provided written informed consent before the study began. Both studies involved the use of a processed EEG for research purposes only and clinicians were blinded to the data. The randomized controlled trial consisted of two groups; the interventional group received EEG guided anesthesia while the anesthesia team was blinded to the monitor in the standard care group. The standard care group consisted of the same methodology that was used in the observational study. Only a subset of patients from the standard care group were included in this analysis due to the labor intensive nature of the visual analysis of long durations of raw EEG data. Patients included in this analysis were randomly chosen from the observational study and standard care group of the randomized controlled trial. The scoring clinicians were blinded to the processed EEG output.

2.2 Measurement of duration of burst suppression

Before the induction of anesthesia, the SedLine® leads were placed on the forehead of the study patients. The monitor contains six electrodes placed in regions approximating F7, F8, Fp1, and Fp2 of the international 10–20 system along with midline (Fz) and ground electrodes. The SedLine® monitor intraoperatively stored the EEG waveform data and generated a burst suppression ratio (BSR). Postoperatively, EEG waveforms were extracted and stored on an USB drive and exported as European Data Format (EDF) files and the time-stamped indices (including BSR) as comma-separated values (CSV) files were retrieved. The EDF files were read using the Prana Software Suite (https://www.phitools.com/prana.php).

The EEG recording for the entire surgical duration was divided into 30-s epochs. Two trained neurologists (RZ and LA) and three trained research staff members (DP, DT, MW) reviewed each 30-s epoch off-line, in pairs. We determined the duration of burst suppression through a consensus between the two investigators, and the neurologists further validated any readings performed by the research staff. Burst suppression was defined as an isoelectric waveform with less than ± 10 μV amplitude across each lead. In instances where a single lead presented mild activity beyond ± 10 μV, neurologist discretion was exercised by considering the level of suppression across the other leads. The duration of burst suppression for each 30-s epoch was determined to the nearest second (0–30 s). An example of an epoch with significant burst suppression is shown in Fig. 1.

2.3 The BSR conversion algorithm

We developed an algorithm to convert the continuous BSR value generated by the SedLine® into a binary time series of 1's (suppression) and 0's ("burst," i.e., non-suppressed) that indicate the EEG state within that particular segment time (as determined by the SedLine®). BSR values are output by the SedLine® every 1.2 s (1/50th or 2% of 60 s) and the segment of time between each of the BSR values is determined to be either suppressed or non-suppressed (binary 1 or 0) through proprietary software. Effectively, the BSR represents a moving average of 1's and 0's, which gives the percent of the prior 50 1.2-s intervals that were classified as suppressed.

This algorithm determines whether the current BSR value (BSR_n) will have a corresponding suppression value (SV_{n-1}) by a 1 or 0 by comparing it to the previous BSR value (BSR_n) as follows:

$$if\ BSR_{n-1} < BSR_n \rightarrow SV_n = 1 \tag{I}$$

$$if\ BSR_{n-1} > BSR_n \rightarrow SV_n = 0 \tag{II}$$

$$if\ BSR_{n-1} = BSR_n \rightarrow SV_n = SV_{n-50} \tag{III}$$

where

$$BSR_n = 100 \cdot \frac{SV_n + \cdots + SV_{n-49}}{50} \tag{IV}$$

and

$$BSR_{n-1} = 100 \cdot \frac{SV_{n-1} + \cdots + SV_{n-50}}{50} \tag{V}$$

If $\mathrm{BSR_n}$ increases from $\mathrm{BSR_{n-1}}$ (I), it must be the case that the SedLine® determined $\mathrm{SV_n}$ to be 1. If $\mathrm{BSR_n}$ decreases from $\mathrm{BSR_{n-1}}$ (II), it must be the case that $\mathrm{SV_n}$ is 0. However, if $\mathrm{BSR_n}$ is the same as $\mathrm{BSR_{n-1}}$ (III), a further determination must be made. Notice from (IV) and (V) that the only values that differentiate the composition of $\mathrm{BSR_n}$ and $\mathrm{BSR_{n-1}}$ are $\mathrm{SV_{n-1}}$ and $\mathrm{SV_{n-50}}$, respectively. It is then the case that if $\mathrm{BSR_n}$ and $\mathrm{BSR_{n-1}}$ are equal, then $\mathrm{SV_n}$ and $\mathrm{SV_{n-50}}$ are also equal.

2.4 Factors affecting the concordance of BSR and visual measurements

All cases were also visually reviewed a second time by a single investigator and assessed for the presence of signal artifacts that may have led to an inaccurate reading by the SedLine® monitor or which made it difficult to assess visually. There are many potential sources of EEG artifact, most commonly patient muscle activity, electrical equipment, and direct physical disruption (movement artifacts) of the leads [12]. Different sources of artifact manifest in different artifact patterns on the EEG waveform, although it is not feasible to definitively determine the source from raw EEG alone. This study defined an artifact in the EEG waveform for a 30-s epoch to be significant if it persisted for more than 3 s.

Because the SedLine® sensor was placed on the patients' foreheads, we investigated whether surgical position would impact the accuracy of the monitor's burst suppression measurements. Surgical cases were stratified into prone or supine based on the actual patient position during surgery. When examining the surgical position, procedure start time was used (as opposed to induction) to account for the fact that patients were induced while supine before being repositioned to prone position for the procedure. We also investigated other potential co-variates that may have affected the processed EEG monitoring of burst suppression, such as the patient's age.

2.5 Statistical analysis

Pearson's correlation coefficients were obtained to assess consistency between the two measurements. In determining whether the two measurements agreed sufficiently with one another, an alternative approach based on graphical techniques and a simple calculation called the 95% limits of agreement [13] was also applied to each group of epochs. We calculated the mean and standard deviation (SD) of the differences between the two measurements and obtained the 95% limits of agreement by the mean difference ± 1.96 SDs. We expect 95% of the differences between measurements by the two methods to lie between these limits. With the consideration that each patient has over 100 observations, we estimated the limits of agreement by a components of variance technique [13]. In addition, we considered the measurements as binary outcomes, i.e., 0 (estimate of burst suppression = 0 s) and 1 (estimate of burst suppression ≥ 1 s(s)), and calculated sensitivity and specificity using the neurologists' assessments as the reference standard. We applied a generalized estimation equation to estimate sensitivity and specificity to account for the repeated measurements within each patient. To determine the impact of signal artifact on estimate consistency, the analysis was performed again after removing epochs with significant signal artifacts.

To check whether the consistency was related to the patients' characteristics, the Wilcoxon rank sum test was applied to compare the correlation coefficients or sensitivity/specificity or lower/upper 95% limits of agreement separately between the younger vs. older and supine vs. prone patient groups. Statistical significance was considered for p-value < 0.05. Multiple testing adjustment was performed by Bonferroni correction within the same category of variables. All analyses were performed using the R statistical computing software (http://www.r-project.org).

3 Results

We reviewed 25,804 30-s epochs (215 h) across 45 patients; patient characteristics are summarized in Table 1. None of the patients included in the study received total intravenous anesthesia (TIVA), with all patients received a balanced technique consisting of volatile anesthetics plus propofol.

The median duration of burst suppression by patient was 15.4 min (IQR = 1.0–20.1) vs. 16.1 (IQR = 0.3–19.7) for the machine *vs.* the neurologist visual assessment, respectively. Table 2A shows the analysis of the epochs as one single collection of individual measurements. The correlation coefficient between the two methods was 0.87 (95% CI 0.868, 0.874 | Fig. 2, Table 2A). Overall, the machine had a sensitivity of 0.94 and a specificity of 0.93 when neurologist readings were considered as the reference standard (Table 2A). The Bland–Altman analysis (Fig. 3, Table 2A) revealed the 95% limits of agreement (LoA) to be − 4.86 to 5.04 s, which means that 95% of the difference from the neurologist reading to the machine estimations lies within that range. The same analysis was performed after removing all epochs with significant signal artifacts (2748 or 11.5% of total epochs); however, neither the correlation coefficient, 95% limits of agreement, sensitivity, or specificity were significantly different (Table 2A).

To assess if the consistency was different between patients in supine vs. prone surgical positions, we calculated the correlation coefficient, 95% LoA, sensitivity, and specificity for each patient. We then compared those measurements as patient metrics between the groups (Fig. 4). The 95% LoA of supine patients was significantly narrower than that of prone patients (− 1.36 to 1.13 s vs. 4.24 to 3.82 s, p = 0.001). Patients who were prone during surgery had significantly lower sensitivity (0.86 vs. 0.97, p = 0.038) than patients who were supine; however, the specificity—while also being lower in prone patients—was not statistically significantly different (0.95 vs. 0.99, p = 0.334) (Fig. 4, Table 2B). Similarly, we compared those consistency metrics between older and younger groups (< 65 vs. ≥ 65). For older patients, the machine-generated estimates had a significantly lower sensitivity (0.92 vs 0.96; p = 0.021) and specificity (0.88 vs 0.99; p = 0.007) when compared with younger patients (Fig. 4, Table 2C).

4 Discussion

This study provides novel information as a follow-up to our prior study, which found that the machine-generated BSR generally underestimated the burst suppression across entire surgery cases when compared to neurologist consensus. When using a more precise estimation of burst suppression by neurologists (to the nearest second vs. only rounding down to 0, 10, or 20 s) and comparing those estimates to machine-generated estimates in smaller time increments (30-s epochs), we found that the sensitivity and specificity for the machine are high when compared to the gold standard (neurologists' visual estimation of duration of burst suppression). While signal artifact did appear to have a slight negative impact on the SedLine® device's accuracy, this impact was not shown to significantly affect the discrepancy between the machine and neurologist readings. Patient age and surgical positions were shown to affect the machine's accuracy in measuring burst suppression. Our results suggest that machine-generated estimates of burst-suppression in older patients and patients in prone surgical position have a lower degree of accuracy when compared to those of patients in supine positions or of a younger age.

The finding that machine-generated BSR estimations are less accurate for older patients could be due to age-related changes in brain structure and function. A previous study, which also utilized the SedLine® monitor, outlined that commercial EEG-based depth-of-anesthesia indices do not account for age-related brain changes. The researchers observed that the proximate sources of age-related EEG changes were an overall reduction in signal power, especially compromised alpha band oscillations in addition to a higher incidence of burst-suppression [14]. The possible underlying physiological causes given for these observations included age-related cortical thinning, brain volume reduction and decreased skull conductivity [15, 16]. These investigators also noted that cortical thinning and brain volume are known to increase distance between the cortical surface and the scalp and that both this increased distance and the resulting cerebrospinal fluid (CSF) which fills the space can impact the EEG signal [17, 18].

This shift in CSF may also be potentially relevant to our finding that the SedLine® BSR was less accurate for prone surgical patients. It has been reported that brain shift and the resulting small changes in CSF layer thickness, induced by changing the subject's position, have a significant effect on EEG signal magnitudes [17]. Specifically, when a patient was moved from a supine to prone position, gravity will move the brain towards the front of the skull. The decreased distance of the brain from the skull, in addition to the reduction in CSF, was shown to have a potential increase in power of up to 58.8% [17]. This potential increase in power for patients in the prone position may explain why the sensitivity was significantly lower, as the increased signal intensity may have made the EEG signal more likely to surpass the voltage threshold for the BSR algorithm, which could in turn lead to a reduced detection rate of burst-suppression and hence more epochs categorized as false negatives. However, these are mainly theoretical considerations and should only be considered as speculative and need to be proven in future investigations. Other potential explanations for the lower sensitivity of the BSR in patients placed in prone position may be due to changes in the impedance of the electrodes, poor grounding, or other motion artifacts.

4.1 Comparison with previous studies

To our knowledge, the only prior study to compare the accuracy of processed EEG in detecting burst suppression using an off-line analysis was work from our previous study, which categorized the degree of suppression in the 30 s EPOCH in 10-s increments. In contrast to our previous work, the current off-line analysis used a continuous measurement rounded off to the nearest second, which is closer to how BSR is computed and likely improved the concordance between the two methods. Furthermore, this is the first study to investigate how surgery characteristics may impact this discrepancy. One potential factor for the absence of similar literature is the labor-intensive nature to visually analyze continuous EEG recordings in 30-s epochs, which was used as a reference standard. This current study differs from our prior work in that more rigorous epoch measurements were implemented (to the nearest second, rather than in 10-s durations) and also assessing the potential reasons for the discordance.

4.2 Clinical implications

Our present results provide potentially important information in terms of the accuracy of processed EEG in measuring burst suppression. It should be noted that burst suppression is not a normal EEG pattern and should be avoided in general. However, although intraoperative burst-suppression has been shown to be associated with postoperative delirium, there has been no study which demonstrated that reducing intraoperative burst suppression results in a reduction in postoperative delirium. Furthermore, the mechanism explaining this relationship is still undefined. Equally unclear is whether postoperative delirium can be reduced by a reduction in the amount of anesthetic doses with the intention of reducing burst suppression. Our previous study showed that EEG guided by anesthesia was associated with less burst suppression particularly in patients with lower cognitive status, however we did not find a statistically significant difference in delirium occurrence between the interventional (EEG guided anesthesia) and standard care groups because we did not have sufficient patients with impaired preoperative cognitive status [6]. Our current results suggest that future investigation on the relationship between burst suppression as monitored by processed EEG and delirium should include patient related factors that may influence the accuracy of machine derived burst suppression such as patient’s age and surgical position. Furthermore, published trials relied on real-time measurement of burst suppression by anesthesiologists [19], the accuracy of which has not been demonstrated when compared to off-line measurements. Our present results suggest that burst suppression generated by processed EEG has accuracy and that any future randomized controlled trials aimed at modifying burst suppression may utilize the automatically generated BSR as markers of burst-suppression.

4.3 Limitations

We had a large number of epochs for comparison; however, the patient sample size was only 45. Because of the study methods’ labor intensity, it was prohibitive to include a larger number of patients. Second, we could not determine the precise causes of the artifacts that may have affected the EEG recordings because the EEG data were analyzed off-line, and we did not have an observer present throughout the entire surgery duration.

Third, although we demonstrated the accuracy of SedLine®'s BSR in estimating burst suppression duration, we did not measure the accuracy of real-time intraoperative visual analysis of burst suppression using waveforms alone. It is unclear whether an intraoperative real-time analysis of raw EEG waveforms would be as accurate as off-line measurements. Finally, this study's primary objective was to compare the two methods of estimating burst-suppression duration, the non-normal distributions of the differences between epochs prohibited parametric statistics when assessing discordance. This non-normal distribution was the primary motivation for a definition for agreement, which provided a binary metric to analyze the data deriving specificity and sensitivity.

4.4 Conclusion

In conclusion, our results suggest that the SedLine®'s BSR can be effectively utilized as a general estimate of burst-suppression. Our results also suggest that both patient's age and the surgical position may influence the monitor's accuracy in determining burst suppression. As more studies elucidate the mechanism between intra-operative burst suppression and post-operative cognitive changes, the automated measurement of intra-operative burst suppression through automated processed EEG could become an increasingly valuable tool for clinicians, as well as a useful tool for researchers. Thus, further studies are necessary to determine what surgical circumstances and patient characteristics may influence processed EEG accuracy so that it can be utilized effectively in both a clinical and research environment.

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Data availability

The data and material used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

The code used during the current study are available from the corresponding author on reasonable request.

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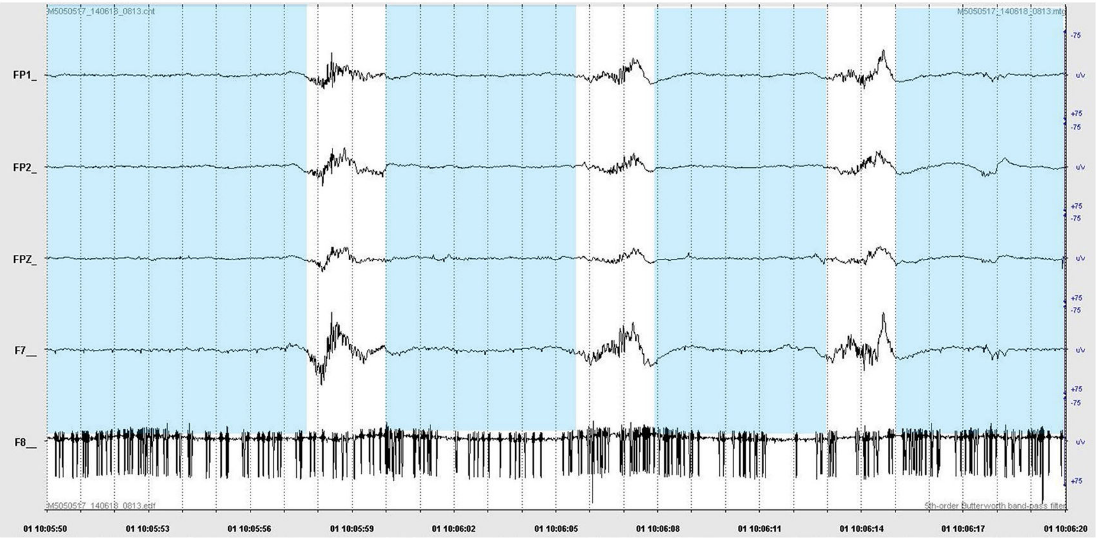

Fig. 1.

Burst suppression pattern with pronounced suppression (highlighted in blue). The total duration of suppression across this epoch was determined to be 21 s

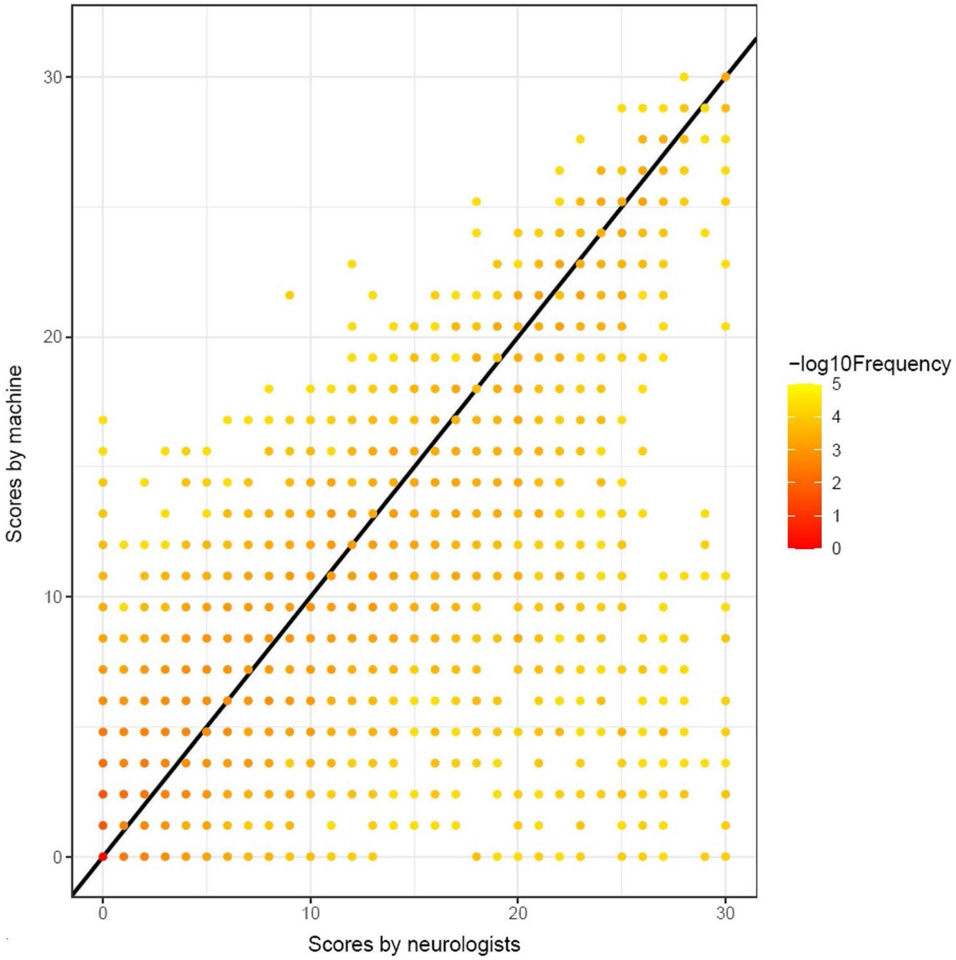

Fig. 2.

Density scatterplot showing how the distribution of seconds of burst suppression differs between the neurologist and machine estimates, for all individual 30-s epochs from all 45 patients

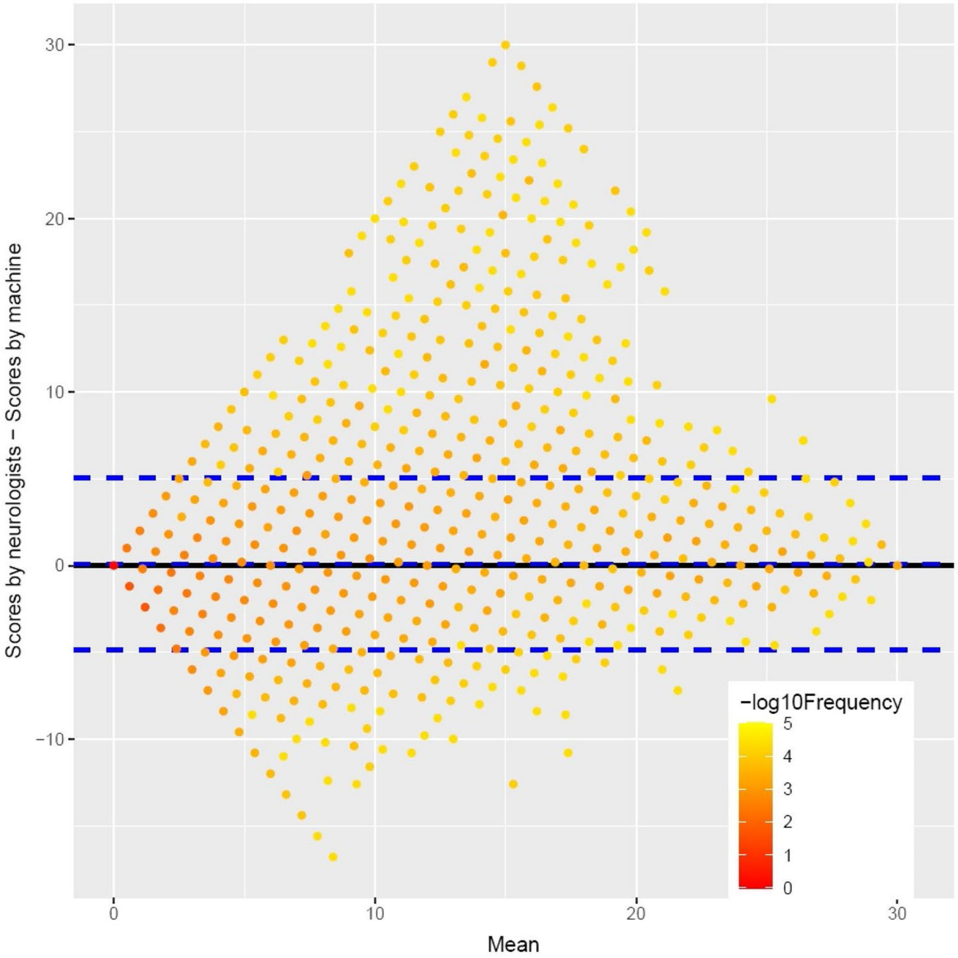

Fig. 3.

Difference-mean plot (difference = [neurologist score – machine score]) showing the relationship between the difference and mean between the two estimation (neurologist and machine) for each individual 30-s epoch. The 95% limits of agreement (LoA) are shown as the two dashed blue lines

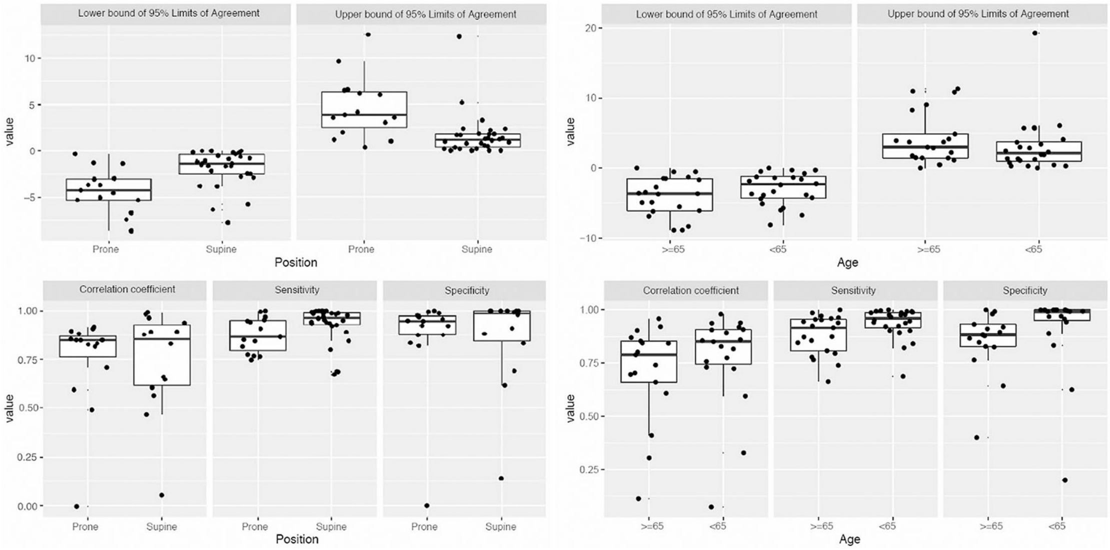

Fig. 4.

Box plots showing the distribution of consistency metrics (Table 2) by surgical position (left) and patient age (right)

Table 1

Patient's characteristics

Total patients	n = 45
Age mean ± SD	64.1 ± 9.5
65 & older	n = 21
Under 65	n = 24
Sex n (%)	
Female	21 (47%)
Male	24 (53%)
Surgery type n (%)	
Spine	19 (42%)
Abdominal	14 (58%)
Thoracic	9 (20%)
Vascular	3 (7%)
Surgery position n (%)	
Prone	15 (33%)
Supine	30 (67%)

Table 2

Consistency metrics: correlation, sensitivity, specificity, upper/lower bound of 95% limit of agreement

	Correlation coefficient (95% CI)	95% limit of agreement	Sensitivity	Specificity
A: Analysis of entire collection of epochs				
All epochs	0.87 [0.87, 0.88]	[− 4.85, 5.03]	0.94	0.93
Epochs w/o artifact	0.89 [0.89, 0.89]	[− 4.49, 4.59]	0.94	0.94

Surgical position (median [range])	Prone (n = 15)	Supine (n = 30)	p-value
B: Comparison of consistency metrics by surgery position			
Correlation coefficient	0.85 [0.00, 0.92]	0.85 [0.05, 0.99]	0.694
Sensitivity	0.86 [0.74, 1.00]	0.97 [0.67, 1.00]	0.038
Specificity	0.95 [0.00, 1.00]	0.99 [0.14, 1.00]	0.334
Lower bound of 95% limit of agreement	− 4.24 [− 8.65, − 0.34]	− 1.36 [− 7.75, 0.00]	0.001
Upper bound of 95% Limit of Agreement	3.82 [0.32, 12.50]	1.13 [0.00, 12.30]	< 0.001
Patient age (median [range])	**65 & older (n = 21)**	**Under 65 (n = 24)**	**p-value**
C: Comparison of consistency metrics by patient age			
Correlation coefficient	0.79 [0.11, 0.96]	0.85 [0.07, 0.98]	0.211
Sensitivity	0.92 [0.66, 1.00]	0.96 [0.69, 1.00]	0.021
Specificity	0.88 [0.40, 1.00]	0.99 [0.20, 1.00]	0.007
Lower bound of 95% limit of agreement	− 3.67 [− 8.88, 0.00]	− 2.32 [− 8.12, 0.00]	0.169
Upper bound of 95% limit of agreement	2.96 [0.00, 11.31]	2.12 [0.00, 19.27]	0.215

95% limits of agreement: 95% of the differences between the neurologist and machine estimations fall within the upper and lower bound of the 95% limit of agreement

A: Consistency metrics were for the entire combined group of epochs for all patient volunteers

B/C: Consistency metrics were determined for each patient between the neurologist and machine estimations of burst suppression, and then groups by surgery position (B) and age (C)