ORIGINAL CLINICAL RESEARCH REPORT

Impact of Age on the Occurrence of Processed Electroencephalographic Burst Suppression

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BACKGROUND: Patient age is assumed to be an important risk factor for the occurrence of burst suppression, yet this has still to be confirmed by large datasets.

METHODS: In this single-center retrospective analysis at a university hospital, the electronic patient records of 38,628 patients (≥18 years) receiving general anesthesia between January 2016 and December 2018 were analyzed. Risk factors for burst suppression were evaluated using univariate and multivariable analysis. We measured the incidence of burst suppression as indicated by the burst suppression ratio (BSR) of the Entropy Module, the maximum and mean BSR values, relative burst suppression duration, mean volatile anesthetic concentrations, and mean age-adjusted minimum alveolar concentrations (aaMAC) at burst suppression, and cases of potentially misclassified burst suppression episodes. Analyses were done separately for the total anesthesia period, as well as for the Induction and Maintenance phase. The association with age was evaluated using linear and polynomial fits and by calculating correlation coefficients.

RESULTS: Of the 54,266 patients analyzed, 38,628 were included, and 19,079 patients exhibited episodes with BSR >0. Patients with BSR >0 were significantly older, and age had the highest predictive power for BSR >0 (area under the receiving operating characteristic [AUROC] = 0.646 [0.638–0.654]) compared to other patient or procedural factors. The probability of BSR >0 increased linearly with patient age (ρ = 0.96–0.99) between 1.9% and 9.8% per year. While maximal and mean BSR showed a nonlinear relationship with age, relative burst suppression duration also increased linearly during maintenance (ρ = 0.83). Further, episodes potentially indicating burst suppression that were not detected by the Entropy BSR algorithm also became more frequent with age. Volatile anesthetic concentrations sufficient to induce BSR >0 were negatively correlated with age (sevoflurane: ρ = −0.71), but remained close to an aaMAC of 1.0.

CONCLUSIONS: The probability of burst suppression during general anesthesia increases linearly with age in adult patients, while lower anesthetic concentrations induce burst suppression with increasing patient age. Simultaneously, algorithm-based burst suppression detection appears to perform worse in older patients. These findings highlight the necessity to further enhance EEG application and surveillance strategies in anesthesia. (Anesth Analg 2024;XXX:00–00)

KEY POINTS

- **Question:** What is the relationship between age, automated burst suppression detection, and anesthetic concentrations?
- **Findings:** The probabilities of burst suppression incidence and relative burst suppression duration increase with patient age, potentially erroneous burst suppression episodes are more common in old patients, and volatile anesthetics lead to burst suppression at lower concentrations with increasing age.
- **Meaning:** Age shows the strongest association with automated burst suppression detection, but processed indices appear to perform worse in these patients and the age-adjusted minimum alveolar concentration (MAC) might not be an appropriate tool to avoid burst suppression.

A minimum of 321 million surgical procedures are performed yearly and a considerable percentage will involve general anesthesia.[1] Due to changing demographics, the number of geriatric patients requiring general anesthesia will likely increase further. Approximately 30 years

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ago, monitoring devices were introduced that used electroencephalographic (EEG) information to quantify a patient's hypnotic state under general anesthesia.[2] These monitors (ie, bispectral index (BIS),[2,3] patient state index,[3,4] state and response entropy (SE/RE)[5]) present a dimensionless index that correlates with the level of consciousness. The index algorithm tracks the anesthetic-induced changes from a frontal EEG. With increasing anesthetic concentrations, the EEG can change toward alternating episodes of isoelectric EEG and EEG bursts, termed burst suppression (BSupp).[6] BSupp, especially when observed during anesthesia maintenance at low anesthetic concentrations, is associated with an increased risk of adverse outcomes, such as postoperative neurocognitive disorders (PNDs).[7–10] Older patients are at higher risk for PND and may be more susceptible to BSupp.[11,12] The monitoring systems use algorithms to identify BSupp and present them as the burst suppression ratio (BSR).[3,13] We will refer to BSupp identified by the GE Entropy algorithm as BSR and use BSupp when describing the general phenomenon. These algorithms are designed to detect the isoelectric EEG episodes, indicative of BSupp.

In this study, we analyzed BSR information of 38,628 adult patients (≥18 years) receiving general anesthesia. We determined the incidence of positive BSR as a function of patient age. Furthermore, we investigated the association between positive BSR and anesthetic concentrations expressed as age-adjusted minimum alveolar concentration (aaMAC) values. Hopefully, these insights will contribute to the development of new strategies for optimizing intraoperative patient monitoring based on EEG recordings.

METHODS

Ethics Approval

The institutional ethics committee of the faculty of Medicine of the Technical University of Munich, Germany approved the study on December 12, 2018 (No. 572/18s; chairperson: Prof Schmidt) and waived the requirement for written informed consent of patients or the next of kin. Electronic records of 88,979 patients receiving general anesthesia at the University Hospital Rechts der Isar, Technical University of Munich, between January 2016 and December 2018 were included in the analysis. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Electronic Records

The electronic records contained the data of BSR, SE, and RE from the Entropy Module (GE Healthcare), as well as concentrations of volatile anesthetics with MAC values from the anesthesia machines, recorded during noncardiac surgeries with a 10 seconds resolution. The records further included information regarding the patient's age, sex (male/female), body weight (kg), height (cm) and body mass index (BMI, body weight [kg] height [m^{-2}]), surgery and anesthesia durations (minutes), the American Society of Anesthesiologists (ASA) physical status classification system, and the specialty conducting the surgery. All patients at least 18 years old were included. Propofol concentrations from total intravenous anesthesia were not analyzed. Importantly, we disregarded additional pharmacological interventions (eg, catecholamines, analgesics, or neuromuscular blocking agents). The records also contained the time points of events, including (i) start of anesthesia, (ii) anesthesiologic clearance for surgical preparations, (iii) start of surgery, (iv) end of surgery, and (v) end of anesthesia.

aaMAC values were calculated with Mapleson's formula,[14] using volatile anesthetic concentrations and patient age from electronic records.

To avoid potential sources of bias, selection of patient records was primarily based on availability of complete datasets for SE, RE, and BSR. We only included records with at least 90% complete data within our observation periods of interest (patient records which had >10% missing data for SE, RE, and BSR were excluded). These periods were based on timestamps recorded in the electronic records, adhering to the standards of the German Perioperative Procedural Time Glossary.[15] Our periods of interest were defined as follows: the (i) total anesthesia period (Total), defined as the start of anesthesia to end of anesthesia, (ii) anesthesia Induction (the start of anesthesia to anesthesiologic case clearance for surgical preparations, Induction), and (iii) the maintenance period (the start of surgery to end of surgery, Maintenance). Compared to Induction, the Maintenance phase is less likely to include wash-in and washout phases of volatile anesthetics or bolus applications of intravenous hypnotics.

Information Extracted From the Records

Based on the availability of complete datasets, we extracted the following information: (i) the incidence of BSR >0, that is, any BSupp detected by the Entropy Module, (ii) the maximum BSR value, (iii) the mean BSR value, (iv) the mean aaMAC and (v) mean volatile concentration (Vol.%) when BSR >0, (vi) the relative duration of BSR >0 (which is calculated as the time spent with a BSR >0 during the anesthesia Maintenance period, divided by the total duration of the Maintenance period for each patient), and (vii) the incidence of an SE >80 at an aaMAC >0.8 (which may be indicative of misclassified BSR) at the same time point. BSupp EEG undetected by the monitor

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can result in implausibly high SE values despite sufficiently high anesthetic concentrations.[16–18] We limited our search for these constellations to the anesthesia Maintenance period. However, we cannot rule out potentially other explanatory factors, such as EMG interferences or electrical artifacts.

Statistical Analysis

Statistical analysis was performed with MATLAB for Windows Version R2023a (The MathWorks, Inc). Categorical variables are presented as n of patients (%) and were compared using the χ^2 test. Continuous variables were tested for normal distribution by using the Anderson-Darling test and via visual inspection of histograms and quantile-quantile plots. As continuous data in this study displayed skewness, we present them as medians with first quartiles (Q1; 25th percentile) and third quartiles (Q3; 75th percentile). Continuous nonparametric and ordinal data were compared using the Wilcoxon rank-sum test. The statistical plan included a univariate analysis for the Total anesthesia period to assess the association between age and other parameters on BSR incidence. These variables included patient sex, BMI, duration of surgery and anesthesia, ASA status, and the department which performed the surgery. For the univariate analysis, missing data points were not imputed or replaced, but excluded from calculations. In cases of unspecified ASA status, we assigned them to the category "ASA not declared." The category "other departments" accounts for infrequent procedures outside the core surgical facilities. A value of $P < .05$ was considered statistically significant. In case of multiple comparisons, we applied a Bonferroni correction. After excluding missing data points, we calculated AUROC (area under the receiving operating characteristic) metrics to determine the discrimination power of individual parameters using the function *mes* (exactCi) from the MATLAB Measures of Effect Size toolbox,[19] as well as phi correlation coefficients (φ) and point-biserial correlation coefficients (r_{pb}). We investigated the relationship between the dependent, binary variable "occurrence of BSR >0" and age and other potential predictor variables, which showed significant results in our univariate analysis. For this purpose, we conducted a logistic regression analysis with data from the Total anesthesia period, using the MATLAB function *fitglm()*, which automatically excludes missing values from computation. The accuracy of the logistic regression model was assessed with a confusion matrix and calculating the AUROC metric. As the dichotomization of BSR >0 occurrence is an approximation, we further analyzed correlations between age and the probability of BSR >0 (separately for the Induction, Maintenance, and Total period), medians of maximal and mean BSR (for the Total period), relative duration of BSR >0, implausibly high SE values at high aaMAC values (SE >80 and aaMAC >0.8), as well as medians of mean volatile anesthetic concentrations with the respective aaMAC values (for the Maintenance period), at which BSR >0 occurred. For this, we created linear and second-degree polynomial fits with 95% prediction intervals We chose to report the second-degree polynomial fit if it substantially increased the goodness of fit, which we defined as an absolute increase in the R-squared (R^2) value of 0.1 or more. We determined Spearman's rank correlation coefficients (ρ) with 95% confidence intervals (Ci) using a bootstrap method (number of bootstrap samples: 1000), which were conducted exclusively on complete datasets. Patients aged 90 years and above were excluded from model generation due to the considerably smaller sample sizes, which may lead to less representative aggregate values, thereby introducing statistical uncertainty.

RESULTS

Final Numbers and Patient Selection

Between January 2016 and December 2018, 88,979 records were available from patients undergoing surgery under general anesthesia. Of these, BSR and SE trend data were available for 54,266 patients. We found complete BSR, SE, and RE data in 38,628 cases, either during Induction (the start of anesthesia to anesthesiologic case clearance), Maintenance (from the start of surgery to end of surgery), or the Total (the start of anesthesia to end of anesthesia) period.

For the Total anesthesia period, we retrieved complete data for 16,782 cases, with BSR >0 in 10,496 cases (62.5%); for Induction: 26,954 cases, with BSR >0 in 10,351 cases (38.4%); and for Maintenance: 23,035 cases with BSR >0 in 8518 cases (37.0%). See Figure 1A for a flowchart and Figure 1B for the respective histograms. Group allocation was not mutually exclusive and some patients were assigned to multiple groups simultaneously. We surmise that the reason for having fewer cases with complete data in the Total period, as compared to the Induction or Maintenance periods, is that the Total period is more extended. It encompasses not only the Induction and Maintenance phases but also the time between anesthesiologic case clearance for surgical preparations and surgical incision, as well as the time between the end of surgery and the end of anesthesia.

Univariate Analysis

In the univariate analysis, the occurrence of BSR >0 versus its absence was compared across various patient and procedural variables (age, sex, BMI, surgery and anesthesia durations, ASA status, and surgical department) for the Total period, as summarized in Table 1. Patients who developed BSR >0, as compared to those who

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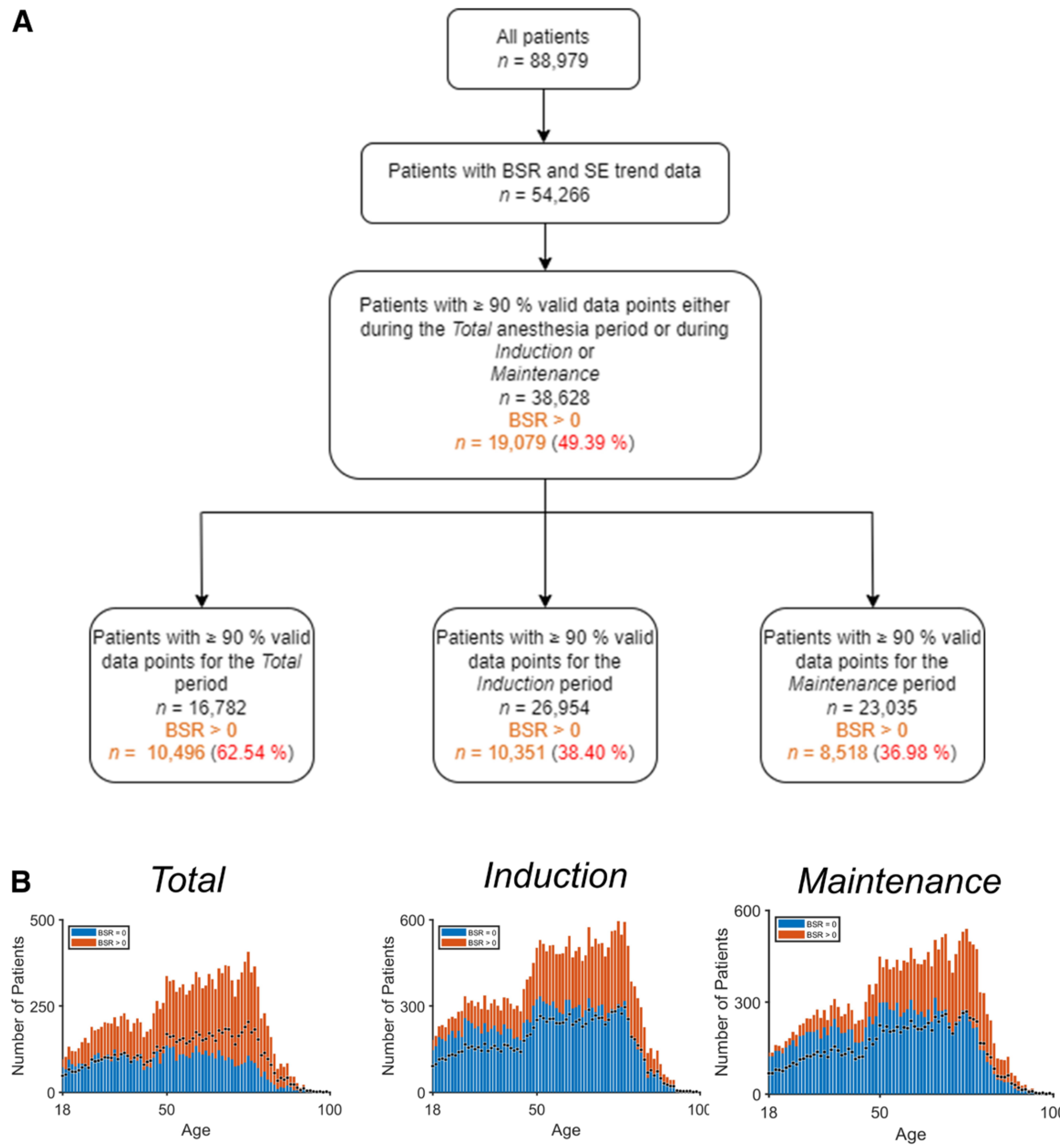

Figure 1. Flowchart with selection of patient data (A) and histograms with the occurrence of BSR >0 in the respective subgroups (B). A, Absolute numbers of patients in black and patients with occurrence of BSR >0 in orange. In red and brackets, percentage of cases with BSR >0 of the respective subgroups. Patients can belong to multiple groups simultaneously, depending on availability of complete datasets. B, Histograms illustrating the frequency of BSR >0 in the respective subgroups, plotted against patient years. Each histogram bar consists of 2 stacked categories: patients who showed BSR >0 are depicted in orange, while those who did not (BSR = 0) are depicted in blue. In each histogram bar, a black dot divides the bar at the 50% length mark. BSR indicates burst suppression ratio; SE, state entropy.

never develop BSR >0, were considerably older with a median age difference of 11 years ($P < .001$). Males were more prevalent in the BSR >0 group, and these patients experienced longer surgeries and anesthesia durations. Significant differences were also observed in ASA status and type of surgery between patients with and without BSR >0. However, the significance of these differences may not directly translate to clinical relevance, considering the large sample size of the study. We therefore calculated AUROC values and correlation coefficients. Collectively, age exhibited the relatively strongest positive correlation (r_{pb}=0.248) and demonstrated the highest discriminatory power (AUROC: 0.646 [95% Ci: 0.638–0.654]) between patients with and without BSR >0 (see also Supplemental Digital Content 1, Supplemental Figure 1, http://links.lww.com/AA/E954). Although our findings indicate a stronger association between age and the incidence of BSR >0 in comparison to other parameters, it is evident that no single parameter surpasses an AUROC value of 0.7, which is considered the threshold for acceptable discriminating ability.[20] Further, we observed that other patient or procedural variables were also influenced by patient age. Specifically, mean ASA values increased with patient

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Table 1. Association Between the Occurrence or Absence of Processed BSR and Patient Characteristics

Variable[a] (unit)	BSR = 0 n	BSR = 0 Median [Q1–Q3]/ (%)	BSR >0 n	BSR >0 Median [Q1–Q3]/%	AUROC [95% CI]	P value[b]	Correlation coefficient[c]
Age (y)	6286	51 [35–64]	10,496	62 [48–73]	0.646 [0.638–0.654]	**<.001**	0.248 (r_{pb})
Sex					0.520 [0.511-0.529]		<0.001 (φ)
Male	3284	(52.24)	5905	(56.26)		**<.001**	
Female	3001	(47.74)	4588	(43.71)		**<.001**	
BMI (kg m^{-2})	5126	25.65 [22.77 – 29.07]	8681	25.44 [22.86 – 28.71]	0.509 [0.500–0.519]	.083	–0.025 (r_{pb})
Surgery duration (min)	6286	67 [33–115]	10,496	80 [42–139]	0.557 [0.548–0.565]	**<.001**	0.079 (r_{pb})
Anesthesia duration (min)	6286	113 [71–170]	10,496	131 [85–202]	0.571 [0.563–0.580]	**<.001**	0.101 (r_{pb})
ASA[d]					0.547 [0.538–0.556]		0.138 (r_{pb})
I	1758	(27.99)	1981	(18.90)		**<.001**	
II	2865	(45.61)	5135	(48.99)		**<.001**	
III	961	(15.30)	2497	(23.82)		**<.001**	
IV	48	(0.76)	144	(1.37)		**<.001**	
V	3	(0.05)	9	(0.09)		.009	
ASA not declared	646	(10.29)	716	(6.83)		**<.001**	
Department[d]					0.518 [0.509–0.527]		
1: Ophthalmology	455	(7.24)	575	(5.48)		**<.001**	
2: General and Thoracic Surgery	868	(13.81)	1624	(15.47)		**<.001**	
3: Obstetrics, Gynecology	1126	(17.91)	1158	(11.03)		**<.001**	
4: Vascular Surgery	291	(4.63)	866	(8.25)		**<.001**	
5: Oral-, Maxillofacial Surgery, Otorhinolaryngology	106	(1.69)	86	(0.82)		**<.001**	
6: Neurosurgery, Spine Surgery	144	(2.29)	364	(3.47)		**<.001**	
7: Orthopedic Surgery	1087	(17.29)	1780	(16.96)		.578	
8: Plastic Surgery	236	(3.75)	664	(6.33)		**<.001**	
9: Urology	933	(14.84)	1697	(16.17)		.022	
10: Trauma Surgery, Hand Surgery	937	(14.91)	1502	(14.31)		.289	
11: Other Departments	103	(1.64)	180	(1.72)		.710	

Bold font indicates statistical significance.Abbreviations: ASA, American Society of Anesthesiologists Physical Status Classification System; BMI, body mass index; BSR >0, occurrence of burst suppression as detected by the algorithm; BSR = 0, absence of burst suppression as detected by the algorithm.
[a]Data from the Total anesthesia period.
[b]Wilcoxon rank-sum test (Mann-Whitney *U* test) for continuous, nonparametric and ordinal variables and χ^2 test for categorical variables.
[c]φ: Phi correlation coefficient. R_{pb}: point-biserial correlation coefficient.
[d]Bonferroni correction for multiple comparisons applied.

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age for the Total anesthesia period. Moreover, patient age varied across surgical departments, as detailed in Supplemental Digital Content 1, Supplemental Figure 2, http://links.lww.com/AA/E949.

Generalized Linear Model

Except for BMI, which showed no statistically significant difference in the univariate analysis, all other examined parameters were incorporated into a generalized linear model. A summary of the logistic regression model's results is provided in Table 2. The χ^2 statistic of the model, when compared with a constant model, is 1040 ($P < .001$). Among all predictors included in the model, patient age was a significant contributor, with a t-statistic of 22.14 ($P < .001$), exerting a substantial cumulative impact over the included age range (18 to 99 years), with a coefficient estimate of 0.026. While both ASA and the surgical department displayed higher coefficient estimates, corresponding to higher per-unit effects on the response variable compared to age, their overall impact is limited by fewer discrete levels. We assessed the performance of our model using a confusion matrix. The model exhibited an accuracy of 64.3% and a precision of 67.7%, with a high sensitivity of 82.1% and a lower specificity of 34.6%. The AUROC, based on the predicted probabilities and quantifying the ability of the model to discriminate between BSR >0, was 0.625 (95% Ci: 0.619–0.631). This finding is quite remarkable, as this generalized linear model reaches a sensitivity of 82.1% without factoring in concentrations of anesthetic agents.

Relationship Between BSR >0 and Age

In the following, we characterize the association between age and BSR parameters, including the probability of BSR >0, observed maximum and mean BSR values, and the relative duration of BSR >0, through

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Table 2. Summary of the Generalized Linear Model

Parameter[a]	Estimate	SE	*t*-stat	*P* value
Age	0.026	0.001	22.14	**<.001**
Sex	0.006	0.036	0.15	.878
Surgery duration	–0.010	0.001	–9.34	**<.001**
Anesthesia duration	0.010	0.001	10.48	**<.001**
ASA	0.062	0.028	2.20	**.028**
Department	0.029	0.006	5.14	**<.001**

Abbreviations: ASA, American Society of Anesthesiologists; BSR, burst suppression ratio; Estimate, logistic regression coefficients; SE, the standard error of the estimate; *t*-stat, *t*-statistic for a 2-sided test.

[a]Relationship between occurrence of BSR >0 and variables with significant results in the univariate analysis. Data from the Total anesthesia period were used for calculations.

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linear and second-degree polynomial regression analyses with correlation coefficient calculations.

Relationship Between Probability of BSR >0 and Age

There was a steady linear increase in the incidence of a BSR >0 (P[BSR >0]) with patient age at every stage of anesthesia, that is, Total, Induction, and Maintenance (Figure 2A–C). The rate of the relative increase in P(BSR >0) ranged between 1.9% and 9.8% annually. The Spearman's rank correlation coefficients (ρ) computed were ρ=0.96 for the Total perioperative phase, ρ=0.98 for Induction, and ρ=0.99 for Maintenance (Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/AA/E954).

Association Between Age and BSR Values

For the 10,496 patients with a BSR >0 during the Total anesthesia period, we found indications that the relationship between age and both maximal BSR and mean BSR could be better described with second-degree polynomial regression fits, which resulted in an increase of 0.1 or more in the absolute R^2 values. Maximal BSR first decreased from age 18 until a nadir of 45.8 years, before the medians of maximal BSR increased with higher patient age (Figure 3A; Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/AA/E954). This observation was more pronounced for the mean BSR, in which case values decreased until 67.3 years before inflecting, sufficiently well-captured by the polynomial fit (R^2 = 0.68); see Figure 3B and Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/AA/E954. Finally, we found a linear increase (R^2 = 0.58, ρ=0.83) in the relative duration of BSR >0 during Maintenance (which is the time spent with a BSR >0 during the Maintenance period, divided by the total duration of the Maintenance period for each patient), see Figure 3C and Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/AA/E954.

Probability of Implausibly High State Entropy Values (>80) at aaMAC >0.8 During the Maintenance Phase

In a subset analysis of 23,035 patients who had complete data during the Maintenance period, we

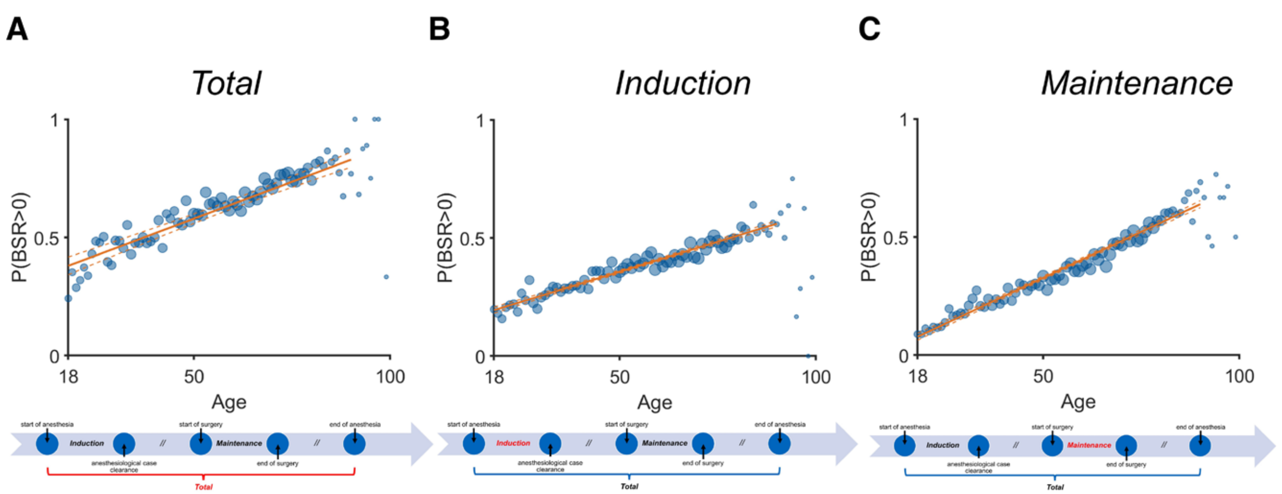

Figure 2. Probability of BSR >0 (P[BSR >0]) as a function of patient age for different anesthesia time episodes.A,P(BSR >0) and linear fit during the entire anesthesia period (Total).B,P(BSR >0) and linear fit during the anesthesia induction period (Induction).C,P(BSR >0) and linear fit during anesthesia maintenance (Maintenance).The dots present the median probability of BSR >0 (P[BSR >0]) for each year of age and the dot size indicates the number of available patients for each year of age. The solid, orange line indicates the linear fit and the dashed, orange lines reflect the 95% prediction interval (calculated for the age range of 18–90 y). A timeline with the defining time points and time periods is shown below. The respective time period is highlighted in red. BSR indicates burst suppression ratio.

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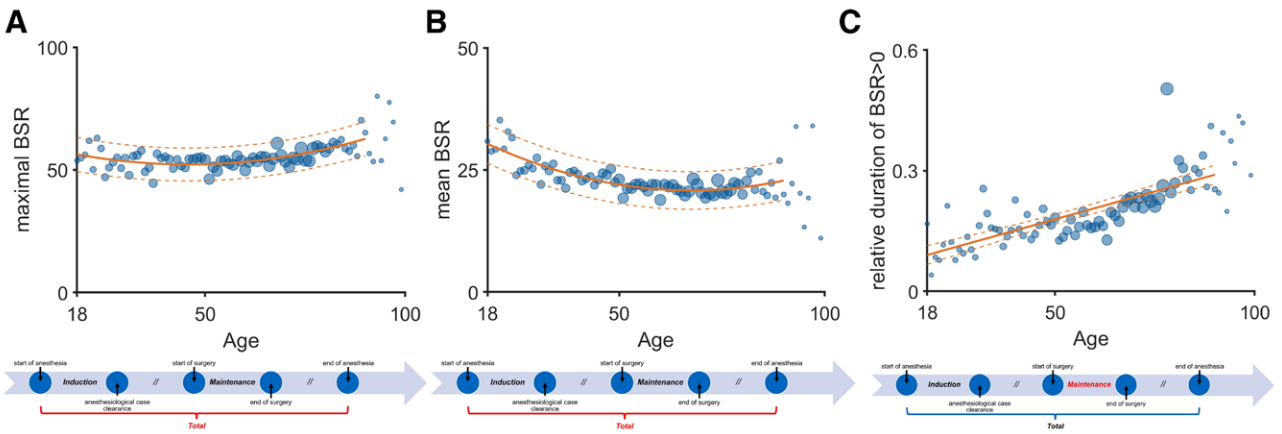

Figure 3. Relationship between age and the BSR features maximal BSR, mean BSR, and relative duration of BSR >0.A,There was a biphasic relationship between age and maximum BSR (Total anesthesia period).B,There was a biphasic relationship mean BSR (Total anesthesia period). C,The relative duration of BSR >0 (time spent in BSR >0 as fraction relative to the total observation period) increased linearly with age during Maintenance. Dots present the median values for each year of age and the dot sizes were scaled according to the patient group count. The solid, orange lines indicate the second-degree polynomial and linear fits. Dashed, orange lines show the 95% prediction intervals (calculated for the age range of 18–90 y). A timeline with the defining time points and time periods is shown below. The respective time period is highlighted in red. BSR indicates burst suppression ratio.

found 500 patients (2.2%) with instances where the data suggested possible undetected or misclassified episodes of BSR >0 (see Figure 4A with the aggregate data and 4B for an exemplary case). Specifically, these cases exhibited high SE values (SE >80) at sufficiently high anesthetic concentrations (aaMAC >0.8). It is crucial to clarify that we can't rule out other factors, like electrocautery-/diathermy-induced artifacts or electromyographic (EMG) changes due to neuromuscular blocking agents.[21] However, this inconsistency between SE and BSR values and the implications have been discussed previously.[16,18]

In the cohort of 500 patients identified with likely false negative instances (unrecognized BSR >0), we further explored the presence of BSR >0 episodes during Maintenance, detected independently of the suspicious findings. 192 patients showed no detected BSR >0 episodes during the entire Maintenance phase. The other 308 patients showed independent instances of BSR >0 at some time during the recording. For context, independent BSR >0 data from these 308 patients were included in broader analyses that covered the 8518 patients showing a BSR >0 episode, making up 3.6% of the Maintenance group. However, the remaining 192 cases were not counted as BSR >0 instances in any analysis.

Lastly, despite some uncertainties regarding the underlying mechanisms, we did find an age-related increase in the incidence of potentially erroneous index values ($P < .001$), as shown in Figure 4A. The linear regression model showed a moderate goodness of fit ($R^2 = 0.47$) with a strong positive correlation (ρ=0.67). The median age of patients with documented "SE >80 and aaMAC >0.8" episodes (66 [54–74] years) was significantly higher compared to patients without this constellation (58 [42–71] years, $P < .001$, AUROC: 0.609 [0.582–0.635], see Supplemental Digital Content 1, Supplemental Figure 3, http://links.lww.com/AA/E954).

Association Between Volatile Anesthetic Concentrations at BSR >0 and Age During Maintenance

From our 23,035 patients included in the Maintenance analysis, 18,085 were administered a volatile anesthetic, and 6612 exhibited a BSR >0 during this period. We could acquire anesthetic concentrations (mean concentrations when BSR >0) and aaMAC values in 4929 instances. We determined the concentrations, at which BSR >0 occurred, and evaluated the association with patient age.

In most cases, sevoflurane was used (n = 4292), while the remaining fraction (n = 637) received desflurane. Regarding sevoflurane, we observed a significant decrease of the mean concentration, at which BSR >0 occurred, with increasing patient age ($P < .001$, $R^2 = 0.47$, $\rho = -0.71$), see Figure 4C. No significant trend was seen concerning the mean aaMAC ($P = .143$, n = 4258), see Figure 4D and Supplemental Digital Content 1, Supplemental Table 1, http://links.lww.com/AA/E954. Interestingly, sevoflurane aaMAC values corresponding with the onset of BSR >0 were mostly around or below an aaMAC of 1.0.

Our sample size for anesthesia Maintenance with desflurane was considerably smaller. However, as for sevoflurane, the mean volatile concentration of desflurane (n = 636), at which BSR >0 was detected, significantly decreased with patient age ($P < .001$,

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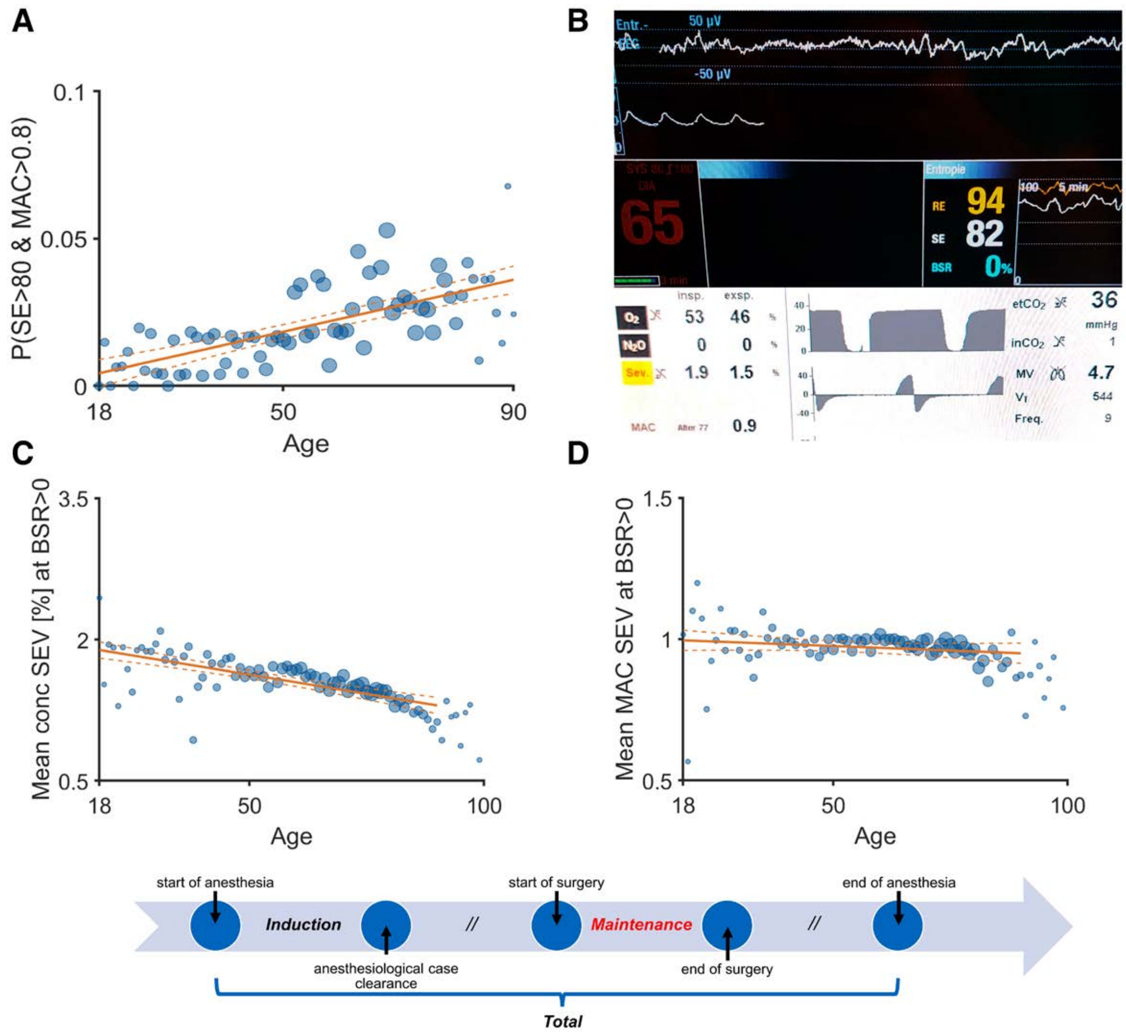

Figure 4. Association between age and potentially erroneous high SE values at high aaMAC concentrations (A), SEV concentrations (C), and SEV aaMAC values (D).A,The probability of potentially erroneous high SE values (SE >80) at sufficiently high anesthetic concentrations (aaMAC >0.8), which could represent misclassified BSR >0 episodes, significantly increased with age (only patients age 18 to 90 included, n = 500).B, Exemplary case of a constellation with SE >80 and an aaMAC >0.8. Stable anesthesia maintenance with adequate anesthetic concentrations (aaMAC of SEV: 0.9, below) of a 77-y-old male patient undergoing surgery. The raw EEG display (scale: −50 to 50 µV) shows BSupp with noisy suppression and low amplitude bursts. However, the Entropy algorithm interprets this EEG pattern as resembling an awake state, as reflected by a BSR of 0% and a RE of 94 and SE of 82.C,The mean Vol.% concentration (conc) of SEV, at which BSR >0 occurred, significantly decreased with age.D,The mean aaMAC of SEV, at which BSR >0 occurred, showed no significant trajectory.Dots present the median value per year and dot sizes were scaled according to the number of patients included for each year. Scatter plots from anesthesia Maintenance period. Linear regression with 95% CI in orange (calculated for the age range of 18–90 y). A timeline with the defining time points and time periods is shown below. The respective time period (Maintenance) is highlighted in red. aaMAC indicates age-adjusted minimum alveolar concentrations; BSR, burst suppression ratio; CI, confidence interval; EEG, electroencephalographic; SE, state entropy; SEV, sevoflurane.

R^2 = 0.28, ρ = –0.49). Again, the mean aaMAC (n = 628) for BSR >0 showed no significant trajectory (see Supplemental Digital Content 1, Supplemental Table 1, Supplemental Figure 4, http://links.lww.com/AA/E954).

DISCUSSION

Our analyses demonstrate a positive correlation between age and the occurrence of BSR >0 in adults. The increase is well described by a linear function. Relative duration of BSR >0 also showed a linear increase, and there was a higher probability of potentially erroneous processed index values with misclassified BSR >0 in older patients. Further, the concentrations of volatile anesthetics sufficient to induce BSR >0 decreased with age and remained close to an aaMAC of 1.0 throughout all age groups.

BSupp is a characteristic pattern in the EEG that develops in the presence of high doses of gamma-aminobutyric acid (GABA)-ergic anesthetics.[22] BSupp seems to reflect a level of excessively "deep" anesthesia associated with an increased risk for PND. However, the nature of this link remains a topic of ongoing debate, as studies showed contradictory results.[23,24] Findings of a recent secondary analysis of the Electroencephalography Guidance of Anesthesia

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to Alleviate Geriatric Syndromes (ENGAGES) trial suggest that the heightened risk for PND was primarily driven by the preoperative cognitive impairment, whereas only about 14% was mediated indirectly by BSupp.[25] As of now, it remains unclear to what extent BSupp directly contributes to PND, or if the concurrent increase in BSupp and PND in older patients is indicative of a shared underlying pathology.

Several predisposing factors are associated with the development of PND and advanced age appears to constitute an independent risk factor.[26] However, these assumptions lack a solid data basis so far and results from pertinent studies were derived from small samples. A post hoc analysis of BIS recordings with 131 patients displaying processed BSupp identified age as an independent risk factor.[27] Based on a study comprising 155 patients, an increase in the probability of BSupp with age was shown.[11] Our analysis confirms these results based on a large dataset and the increase with age appears to be robustly linear. We could also describe this increase independently for the Induction and Maintenance phase. This distinction may be necessary, because the adequacy of anesthetic effects during induction is assessed by cessation of patient response or purposeful movement rather than the onset of BSupp, with marked differences between the required concentrations.[28] This may be because the primary mechanism underlying immobility is spinal,[29] whereas the effects of anesthetics on unconsciousness are attributed to supraspinal mechanisms.[30] Furthermore, data suggest that BSupp during anesthesia maintenance in particular seems to be associated with PND.[9,10]

Another finding of our study was that the concentrations of the inhalational anesthetics needed to induce BSR >0 decreased with advancing age. This aligns with the cognitive frailty concept, suggesting that aging brains are more prone to entering BSupp at lower anesthetic concentrations. A recent study showed that patients with elective surgeries had an increased risk for PND in the intensive care unit when intraoperative BSupp was occurring at lower volatile anesthetic concentrations.[31] Naturally, these results further question the reliability of conventional concentration scales used for navigating general anesthesia, such as the MAC, and point toward the need for adjustments. One study proposes a novel risk score both incorporating aaMAC values and BIS values.[32] Patients with a lower score appear to have a higher risk for PND. As this score relies on the BIS rather than the suppression ratio, the true incidence of BSupp is likely underestimated.[33] Further, patient age substantially influences processed indices, including BIS, which might also be problematic.[34]

Although the age-adjustment of the MAC compensates the decreasing concentrations of inhalational anesthetics sufficient to induce BSR >0, the mean aaMAC, at which BSR >0 occurred, was consistently around or below a value of 1.0 in all age groups. Therefore, adhering to traditional aaMAC values may be inadequate when aiming to avoid BSR >0. For the age-adjustment of the MAC, we used the formula published by Mapleson.[14] In a more recent study,[35] an updated formula was proposed. Despite a high degree of similarity, these new findings should be incorporated in future studies.

All our results were derived from processed EEG information. The processed EEG information regarding BSR >0 may underestimate the actual incidence of BSupp, especially in patients of advanced age.[17,36,37] In some cases, undetected BSR >0 episodes may even lead to erroneously high index values indicative of wakefulness.[17,18] As a result, older patients could be at risk of receiving excessive doses of anesthetics.[38] Therefore, our results might be different from results based on the visual inspection of raw EEG. To correct for undetected episodes, we investigated the prevalence of SE >80 in patients with an aaMAC >0.8. Interestingly, we also found that the occurrence of these episodes increased with advancing patient age, implying that algorithm-based BSR >0 detection may be less reliable in older patients.[16] However, we do want to not overemphasize these findings, as we cannot exclude alternative explanations.

Another biasing factor of our results may have been using the processed EEG per se. Age changes the EEG under general anesthesia with and without BSupp.[11,39,40] The EEG becomes faster and lower in amplitude,[40] which causes an increase in the index of most EEG-based anesthesia monitors.[34] Higher anesthesia indices may partially account for the increased probability of BSR >0 occurrence, potentially due to inappropriately high dosages of anesthetics and a rise in potentially erroneous index values.

It is crucial to understand the processed EEG with all of its benefits and shortcomings. Titrating the anesthetic to an adequate level becomes more difficult in older and frailer brains.[41,42] The next generation of detection algorithms for BSupp should be more reliable by—for instance—not only focusing on the suppression episodes. A recent study showed that a collapse in alpha oscillatory activity may precede BSupp.[43] Until then, clinicians should be cautious not to rely exclusively on processed EEG indices and also develop proficiency in assessing raw EEG. This is particularly important for correctly interpreting situations where the monitor might produce contradictory outputs or potentially misclassify BSupp episodes. This approach was also recommended by the European Society of Anesthesiology and Intensive Care Medicine in the recently updated guideline on postoperative delirium in adult patients.[38]

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Importantly, we want to stress the limitations of this study. Its retrospective nature precludes assumptions about causality and the relationships outlined here are purely descriptive. Notably, the observed age-associated increase in the probability of BSR >0 may be partially confounded by ASA status, as we noted a higher incidence in ASA III and IV patients. A critical factor that remains unaddressed is the interplay between chronological age and physiological age, including brain frailty. Other unmeasured factors likely contributed to the occurrence of BSR >0. Notably, our analysis did not encompass hemodynamic parameters. It was shown that the combination of low mean arterial pressure at low MAC values with low BIS scores leads to a higher mortality risk.[44] Further, this monocentric study only includes data from one hospital, which might have introduced biases. Our findings describing the relationship between age, BSR >0, and anesthetic concentrations of desflurane, as well as age and potentially misclassified episodes should be interpreted with caution. Lastly, this analysis exclusively included adult patients (≥18 years) and its findings should not be generalized to younger age groups.

CONCLUSIONS

In conclusion, adult patients receiving general anesthesia experience episodes of BSR >0 more often with advancing age, for longer periods of time, and at lower anesthetic concentrations. This knowledge can help to develop new concepts for anesthesia navigation in the elderly.

DISCLOSURES

Conflicts of Interest: M. Kreuzer is named as an inventor for a patent dealing with spectral EEG features and age (US Provisional Patent Application No. 62/914,183). G. Schneider and M. Kreuzer are named as inventors for a patent filed on a novel method for intraoperative EEG monitoring (US Patent Application Serial No. 62/960,947). G. Schneider, M. Kreuzer, and S. Kratzer are also named as inventors for a patent dealing with the EEG features during anesthesia emergence (US Provisional Patent Application No. 63/459,294). No other authors declared Conflicts of Interest. **Funding:** None. **This manuscript was handled by:** Lisbeth Evered, BS, MBiostat, PhD.

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