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EEG power spectral density under Propofol and its association with burst suppression, a marker of cerebral fragility

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HIGHLIGHTS

- We designed a score (BP_{TIVA}) assessing cerebral fragility using EEG and Propofol infused doses.
- At a same anesthetic depth, BP_{TIVA} score distinguishes between fragile and normal patients.
- The present score is better associated to burst-suppression than the age variable.

ABSTRACT

Objective: Under General Anesthesia (GA), age and Burst Suppression (BS) are associated with cognitive postoperative complications, yet how these parameters are related to per-operative EEG and hypnotic doses is unclear. In this prospective study, we address this question comparing age and BS occurrences with a new score (BP_{TIVA}) based on Propofol doses, EEG and alpha-band power spectral densities, evaluated for SEF_{95} = 8–13 Hz.
Methods: 59 patients (55 [34–67] yr, 67% female) undergoing neuroradiology or orthopedic surgery were included. Total IntraVenous Anesthesia was used for Propofol and analgesics infusion. Cerebral activity was monitored from a frontal electrodes montage EEG.
Results: BP_{TIVA} was inversely correlated with age (Pearson $r = -0.78$, $p < 0.001$), and was significantly lower ($p < 0.001$) when BS occurred during the GA first minutes (induction). Additionally, the age-free BP_{TIVA} score was better associated with BS at induction than age (AUC = 0.94 versus 0.82, $p < 0.05$).
Conclusion: We designed BP_{TIVA} score based on hypnotics and EEG. It was correlated with age yet was better associated to BS occurring during GA induction, the latter being a cerebral fragility sign.
Significance: This advocate for an approach based on evaluating the cerebral physiological age (« brain age ») to predict postoperative cognitive evolution.

1. Introduction

The ElectroEncephaloGraphy (EEG) is an almost century old non-invasive method deployed for electrophysiological cortical activity investigations. In the forties, it was proposed in the operating room to monitor the depth of anesthesia (Gibbs et al., 1937). Normal brain activity for a healthy and awake subject consists in either the beta ([14–25]Hz) or gamma (>25 Hz) band frequency to alpha-band frequency ([8–13]Hz) when relaxed with closed eyes. These fast oscillations (>8 Hz) possesses a small amplitude reflecting the cortical unsynchronized activity. In contrast, under General Anesthesia (GA), cortical neurons are not involved any more in information processing but are directly driven by a slow and a rhythmic thalamic input. Generally speaking, GA is characterized by an overall reduced neuronal activity and

Abbreviations: BIS, Bispectral Index; BS, Burst Suppression; sGA, General Anesthesia; POD, Post-Operative Delirium; PSI, Patient State Index; SEF, Spectral Edge Frequency; TCI, Target Controlled Infusion; TIVA, Total IntraVenous Anesthesia.

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dominant slow waves in the delta band frequency (<4 Hz), caused mainly by a GABA-A mediated inhibition of brain stem arousal nuclei inputs combined with boosted cortical inhibitory post-synaptic currents (Akeju and Brown, 2017).

In the operating room, the state of GA is monitored through EEG-based neuro-monitoring. EEG quickly became a common tool to monitor the level of awareness and track loss of consciousness, due to its simplicity to setup, low cost and capacity to provide in real-time information about the brain state. An important index extracted from the EEG signal is the Spectral Edge Frequency (SEF_{95}), that has been proposed to evaluate changes in brain states and corresponds to the frequency threshold below which 95% of the signal total power is contained (Rampil et al., 1980). One of the consequences of GA being to reduce the amount of fast wave in EEG signals, the SEF_{95} index is thus a way to roughly estimate the depth of anesthesia. Indeed, Archibald and Drazkowski (1985) first proposed a classification of anesthesia in 3 stages based on the SEF_{95} levels: light (SEF > 15 Hz), moderate (SEF in [8, 13 Hz]) and deep (SEF < 7 Hz) (Archibald and Drazkowski, 1985) suggesting that a stable state of anesthesia hypnosis for surgery is achieved for a SEF_{95} between 8 and 13 Hz (SEF_{95} = 8–13 Hz). We can note that depth of anesthesia indices, including the Bispectral Index (BIS) and the Patient State Index (PSI), widely used in operating rooms, are calculated using the SEF_{95} value.

The extension of EEG monitoring under anesthesia has improved considerably since 1985, reducing at the same time remarkably patients' morbidity. Recently, a lot of effort has been put into studying the intra-operative burst suppression (BS) EEG pattern, characterized by alternating periods of electrical suppressions and periods of polyrhythmic waves of high amplitude (Purdon et al., 2015a, 2015b). It has mainly been reported in patients under deep anesthesia conditions, but BS is also usual in conditions that globally affect brain such as hypothermia and diffuse and severe lesions whatever the etiology (Urrego et al., 2014). BS under GA has been described as an independent risk factor of Postoperative Delirium (POD) (Fritz et al., 2016) which is associated with a long term cognitive decline (Saczynski et al., 2012; Inouye et al., 2016) and with increased morbidity and healthcare costs (Marcantonio, 2017). It is unclear whether intra-operative BS causes POD or merely reflects susceptibility to POD. Thus BS occurrences during EEG monitoring could be viewed as a marker of cerebral fragility in response to a standardized anesthesia, all the more, BS is more frequent in the elderly (Purdon et al., 2015a, 2015b; Besch et al., 2011).

A detailed reading of the quantitative EEG (qEEG) under GA has been recently described depending both on the specific drug used and patients' age. Indeed, GA induced with the hypnotic Propofol (2,6 di-isopropylphenol), a GABAergic receptor agonist used in Total Intra Venous Anesthesia (TIVA), is characterized by a salient alpha-band measured on frontal derivations (Purdon et al., 2015a, 2015b). However, the elderly attenuates these EEG characteristics, which might be the results of a change in thalamic-cortical function and decreased neuronal excitability (Purdon et al., 2015a, 2015b). Indeed, a decrease in signal power in all frequency ranges and more pronounced in the alpha frequency band is clearly found in all subjects over 70 years (Purdon et al., 2015a, 2015b). Young and elderly patients may reach a stable SEF_{95} between 8 and 13 Hz state allowing surgery, but with completely different signal power, especially in the alpha band.

In this study, we proposed a new score named Brain Power spectral density under Propofol-induced Total Intra Venous Anesthesia (BP_{TIVA}), for assessing the fragility of a patient under GA and based on the SEF_{95} = 8–13 Hz period, weighted by the amount of Propofol administered. The hypothesis was that this score would be associated with two criteria of cerebral fragility recognized in the literature: age and burst suppression. Cerebral fragility refers to the risk of developing cognitive dysfunction within the postoperative period. The present paper is organized as follows: first, we have calculated the BP_{TIVA} score for populations of different ages based on the recorded total brain power spectral density (P_T), alpha band power spectral density (P_α) and the amount of Propofol (μg/ml) administered during an SEF_{95} = 8–13 Hz period. Then, we analyzed the relationship between the BP_{TIVA} score and BS occurrence at induction (the first 20 min following the initiation of TIVA) using a logistic regression model.

2. Methods

2.1. Ethics statement

This study was approved by the Institutional Review Board of the Société de Réanimation de Langue Française (CE SRLF 11-356). Exclusion criteria were age <18 years and an emergency procedure. In agreement with the ethics committee for this non-interventional study an information letter was given, and an oral agreement was obtained from each patient before anesthesia. We have obtained a Clinical Trial registration with the following numbers NCT03876379.

2.2. Patients

Between September 2017 and May 2018, patients eligible for interventional neuroradiology or orthopedic surgery performed under GA were selected to participate in this prospective, observational, single-center, routine care study. Patients were included if they received, for a non-urgent scheduled procedure, a Propofol-based TIVA according to the Schnider model (Absalom and Mason, 2017) combined with a morphine derivative. Minor patients, pregnant women and patients who refused to provide informed consent were excluded from the study. Patients with a Body Mass Index (BMI) > 35 kg/m^2 for whom the Schnider model is not validated were also excluded. Patient demographics were collected during the anesthesia consultation.

2.3. Anesthesia procedure

Standard monitoring (Pulse Oxygen Saturation: SpO2, Heart Rate: HR, Systolic, Diastolic and Mean Arterial Blood Pressure: SBP, DBP, MAP, Temperature, End tidal CO_2: EtCO2) and electroencephalogram monitoring by the Masimo Sedline monitor (SEF_{95}, Patient State Index: PSI and BS) were recorded.

General anesthesia was then induced in a standardized manner with a morphine followed by intravenous administration of Propofol according to two separate protocols:

- For neuroradiology patients, remifentanil (Ultiva®) was used as the morphine and the Target Controlled Infusion (TCI) concentration ranged from 5 to 6 ng/ml (depending on the Minto model) until oro-tracheal intubation and then decreased for maintenance to 3–3.5 ng/ml depending on the anesthesiologist's decisions in the operating room.
- For patients included in orthopedic-surgery, the morphine used was sufentanil (Sufenta®) in iterative administration (bolus between 0.2 and 0.3 μg/kg).

Propofol brain TCI was started at 5 μg/ml according to the Schnider model until oro-tracheal intubation for both protocols, yet the anesthesiologist had the possibility to adapt the Propofol concentration at any time. All patients were intubated after curarization by Atracrium (atracurium besilate, 0.5 mg/kg) and mechanically ventilated with a tidal volume of 6–8 ml/kg and a respiratory rate adapted to obtain an $EtCO_2$ between 35 and 38 mmHg. Based on our institution's standard care protocol with the following objectives: PSI between 25 and 40 avoiding as much as possible BS times and MAP > 70 mmHg or 80% of the reference, the administration of fluids, vasoconstrictors and level of sedation was left to the discretion of the anesthesiologist in charge of the patient.

2.4. Per operative EEG collection and data analysis

EEG data were collected from frontal electrodes (Fp1, Fp2, F7, F8), using the Sedline brain function monitor (Masimo Corporation, Irvine, California, USA). Frontal EEG monitoring is both easy to install and routinely used in GA monitoring, besides it captures most of the alpha-band frequency resulting from a Propofol-induced TIVA. Per-operative data such as Patient State Index (PSI), BS and SEF_{95} were collected prospectively using Masimo Instrument Configuration Tool (MICT) software. Raw EEG traces were extracted and analyzed quantitatively using a windowed Fourier transformation embedded in the software EDF browser (experimental viewer and available under GPL version 3 license). The per-operative EEG signal was discarded for electrodes with impedance greater than 5 kΩ. The EEG power spectral density was systematically computed only from the electrode Fp2 arbitrarily chosen in order to simplify the single electrode analysis. Unit of total power of both EEG signal (P_T) and the alpha band (P_α) were expressed in $\mu V^2/Hz$.

Artifacts were limited by patients sedation and curarization (no eye movements or myogram events), possible other type of artifacts were monitored and avoided by an anesthetist trained in reading EEG. To detect regions of iso-electrical suppressions, associated to BS patterns, we built a custom Matlab 2018a threshold detection algorithm where we used the EEG signal collected from the two electrodes Fp1 and Fp2. We averaged the two signals and search for regions characterized by a low signal amplitude in the range of $[-10; 10]$ µV and lasting at least one second (Pilge et al., 2014).

The detection of BS was validated by the eye, for each patient, by an electro-physiologist trained in EEG reading. Concentrations of all drugs administered during general anesthesia were recorded. We were therefore able to determine the maximal concentration of Propofol used for anesthetic induction and the average concentration of Propofol over the rest of the anesthesia.

2.5. Study protocol

We identified three specific periods during general anesthesia that we defined as follows:

1. *Induction Period*: The GA induction period is defined here as the first 20 min following the initiation of Propofol infusion. The presence or not of a suppression period at induction has been detected during this period.
2. SEF_{95} = 8–13 Hz *or Hypnotic Period*: The Hypnotic period is characterized by a period where the SEF 95 ranged between 8 and 13 Hz for at least 5 min, with neither artefacts nor BS. Such period is screened after the induction period and before the surgical incision, besides, we included two additional criteria: first Propofol TCI had to be constant for at least 10 min, secondly, hemodynamic had to be stabilized such that the Mean Arterial Pressure (MAP) is greater than 70 mmHg (3–4).
3. *Total Anesthesia Period*: This period represents the total time spent under general anesthesia, including the induction period. The suppression time in seconds has been determined during this period.

2.6. BP_{TIVA} score: Brain power spectral density under total intra venous anesthesia (TIVA) by Propofol

As previously described, for SEF_{95} = 8–13 Hz periods, the brain total power spectral density (P_T), alpha band power spectral density (P_α) and the Propofol TCI (µg/ml) used could vary from one patient to another. To account for such variability, we have designed a multi-parametric score combining these three parameters. The value and rating scales were arbitrarily chosen by the authors (CT and FV) based on their personal experiences and the available data in the literature (Purdon et al., 2015a, 2015b). Table 1 summarizes conversion of parameters into points, then BP_{TIVA} score was defined as the sum of the three scale values. We can remark that patients with similar SEF_{95} = 8–13 Hz periods, can have a score going from 3 to 12 (from low brain power with low dose of Propofol to high brain power with high dose of Propofol).

2.7. Statistical analysis

The significance level used in this study was $\alpha = 0.05$. The values was expressed in percentage for qualitative variables and median (Inter-Quartile Range: [IQR]) for quantitative variables. All parameters were recorded and BP_{TIVA} score was calculated on the entire population, and also according to the following age ranges: 18–40; 40–65 and >65 years. Then the population was split in two groups according to the median value of BP_{TIVA} score and compared using non-parametric Kruskal-Wallis and Man-Whitney tests for quantitative data, while qualitative variable were analyzed based on the Fisher's test. Research on the correlation between age and BP_{TIVA} score was carried out by Pearson's test. Due to the higher risk of BS during the induction period (transition from awake to anesthetized state over a short period of time requiring a bolus of Propofol) but also because of the ease of standardization of this period, BP_{TIVA} at SEF_{95} = 8–13 Hz has been compared to the presence of BS at induction. Then analysis was also performed according to the occurrence of BS during induction of anesthesia. Receiver Operating Characteristic (ROC) curves were constructed from univariate logistic regressions to test whether BP_{TIVA} score could predict BS occurrence during GA induction and maintenance periods. For each univariate regression, we provided Odd Ratios (OR) given with a 95% Confidence Interval (CI) and Areas Under Curves (AUC) for the ROC curves.

3. Results

3.1. Patients

Ninety patients were selected from September 2017 to May 2018. Five patients were excluded from the analysis due to poor per-operative EEG signal quality. Three patients were excluded because of per-operative ketamine administration, an NMDA antagonizing drug that strongly changes the EEG signal and thus our analysis. A total of 82 per-operative EEGs were analyzed, among which, only 59 (72%) had a SEF_{95} = 8–13 Hz period, Fig. 1. Indeed, 23 patients (28%) never achieved a stable period of SEF_{95} = 8–13 Hz as previously defined after intubation and before surgical incision. Those 23 patients are presented in the Supplementary Appendix.

The median age of the 59 patients was 55 [34–67], where 37 (63%) were women. Patients included had a procedure in neuroradiology 42 (71%) and orthopedic 17 (29%) (Table 2). 24 patients (41%) had at least one cardiovascular risk factor and 30 (51%) had chronic neurological disease (intracranial hypertension, asymptomatic cerebral aneurysms, migraines or epilepsy) without sensorimotor or cognitive impairment. Five patients (8%) had

Table 1
Point scales for P_T, P_α and Propofol concentration during SEF_{95} = 8–13 Hz period.

Score	1	2	3	4	5
$Propofol_{TCI}$ (μg/ml)	<2.5	2.5–3.5	≥3.5		
P_T (μV^2/Hz)	<800	800–1500	1500–3000	>3000	
P_α (μV^2/Hz)	<100	100–200	200–300	300–400	>400

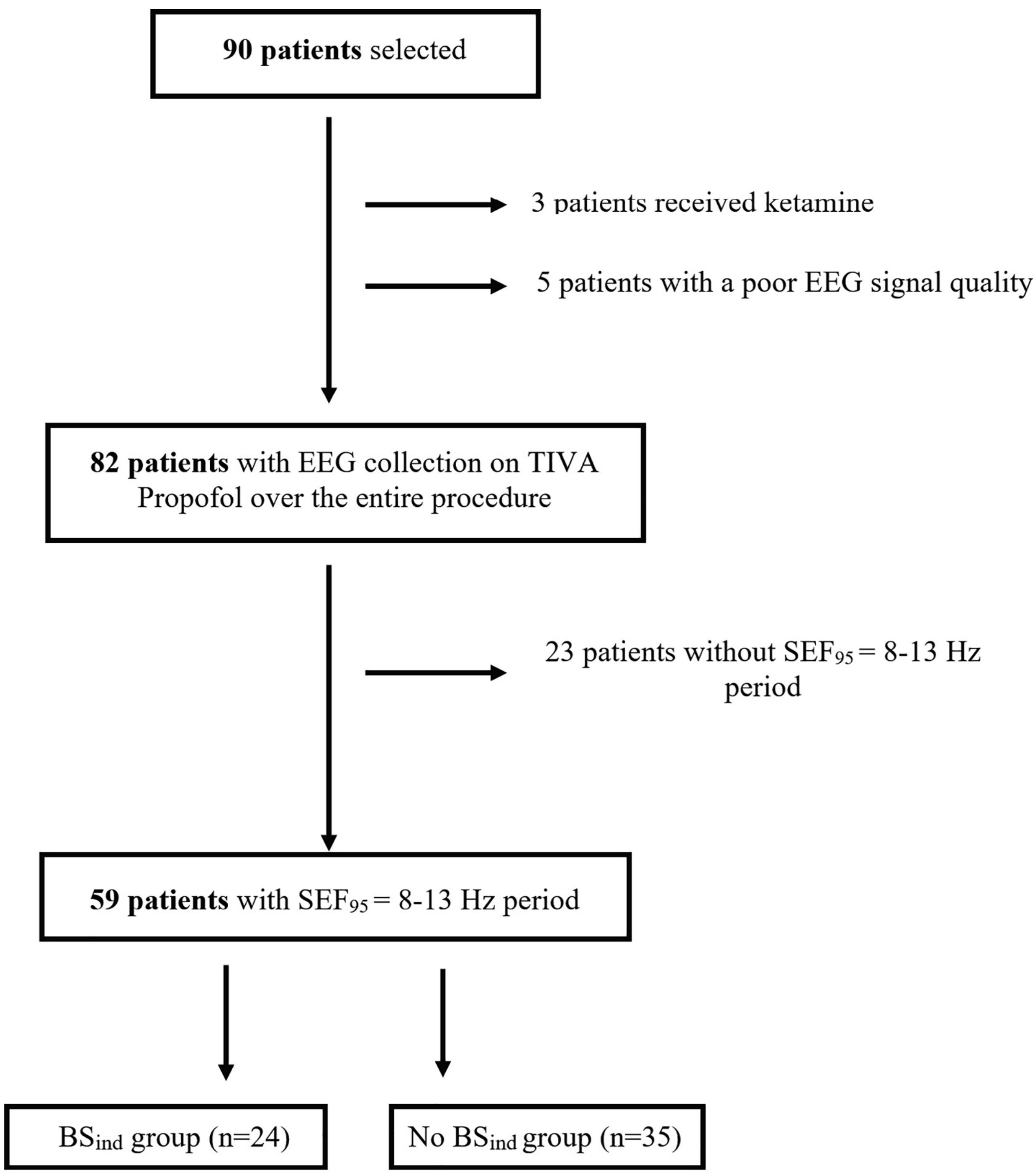

Fig. 1. Patient flow chart for BP_{TIVA} score design.

known pre-operative cognitive dysfunction. The median intervention time was 157 min [120–200].

3.2. BP_{TIVA} during SEF_{95} = 8–13 Hz periods

We were interested in describing the range in BP_{TIVA} score among our patient population (n = 59). We recall that BP_{TIVA} is computed using point scales based on the Propofol Target Controlled Infusion (TCI), the EEG total power (P_T), and alpha-band power (P_α) (see Section 2). During the 5-min period used to calculate BP_{TIVA}, the median SEF 95 of patients was 12 Hz [11.7–12.2] corresponding to a median PSI of 30 [29–32]. Among the 59 patients during SEF_{95} = 8–13 Hz period, Propofol TCI was 3.5 μg/ml [3–3.8], P_T median was 1300 μV^2/Hz [980–2700] and P_α median was 200 μV^2/Hz [110–380] (Table 2). In accordance with the quotation table (Table 1) this gives a median BP_{TIVA} of 8 [6–10] in the overall population. When the population is separated according to this median (Lo-BP_{TIVA} group and Hi-BP_{TIVA} group), we found

Table 2
Characteristics of population.

Number of subjects	All (n = 59)	Age group 1 18–40 (n = 18)	Age group 2 40–65 (n = 20)	Age group 3 >65 (n = 21)	p
Age, median (range)	55 (34–67)	28.5 (21.75–34)	53 (46.25–60)	68 (66.5–74)	
Sexe (male), n (%)	22 (37%)	6 (33%)	9 (45%)	7 (33%)	
MAP baseline (mmHg)	95 (80–105)	85 (80–90)	97.5 (86.25–107.5)	100 (82.5–107.5)	
Intervention n (%)					
Neuroradiology	42 (71%)	17 (94%)	16 (80%)	9 (43%)	
Orthopedic surgery	17 (29%)	1 (6%)	4 (20%)	12 (57%)	
Comorbidity n (%)					
Cardiovascular risk	24 (41%)	5 (28%)	5 (25%)	14 (67%)	
with High Blood Pressure	14 (24%)	0 (0%)	5 (25%)	9 (43%)	
Neurology history	30 (51%)	11 (61%)	11 (55%)	8 (38%)	
Pre-op. cognitive dysfunction	5 (8%)	0 (0%)	1 (5%)	4 (19%)	
Induction					
Burst suppression	24 (41%)	1 (6%)	8 (40%)	15 (71%)	
Propofol concentration (μg/ml)	5 (5–5.375)	5 (5–6.75)	5 (5–5.875)	5 (5–5)	0.0014
Delta MAP (MAP :baseline-lowest)	27.5 (20–35)	20 (15–25)	25 (20–33.75)	35 (30–42.5)	
Maintenance (SEF_{95} = 8–13 Hz)					
Propofol concentration (μg/ml), median (range)	3.5 (3–3.8)	4 (3.5–4)	3.5 (3–3.575)	3 (2.8–3.5)	<0.001
MAP	80 (70–80)	75 (70–80)	80 (71.25–85)	80 (75–80)	0.12
PSI	30 (29–32)	30 (29–33)	30 (28–31)	31 (30–32)	0.14
SEF 95 (Hz)	12 (11.7–12.2)	11.9 (11.6–12.2)	11.8 (11.6–12.1)	12 (11.9–12.3)	
Total power (μV^2/Hz)	1300 (980–2700)	2600 (1825–3950)	1300 (987.5–2650)	980 (570–1350)	<0.001
Alpha band power (μV^2/Hz)	200 (110–380)	462.5 (296.25–587.5)	165 (120–350)	110 (47.5–192.5)	<0.001
BP_{TIVA}, median (range)	8 (6–10)	11 (9–12)	8 (6–9.75)	6 (4–7)	<0.001
Total intervention					
Intervention time (min)	157 (120–200)	162 (133–236,45)	171 (120–194)	129 (104–244)	0.51
Suppression time (s)	10.5 (0–170.5)	0 (0–5.25)	44 (5.5–153)	149 (5.5–319)	≤0.001

that patients in lo-BP_{TIVA} group were older, had more cardiovascular risk factors and more frequent preoperative cognitive dysfunction (Table 3).

A higher percentage of patients in lo-BP_{TIVA} group had at least one event of BS during the induction phase of general anesthesia (81% of them had BS during the induction period versus 8% in those with high BP_{TIVA}). Total per-operative suppression duration were significantly longer in lo-BP_{TIVA} group (103 vs 5 s, p = 0.005) while they had in average significantly lower Propofol TCI (3.1 vs 3.9 μg/ml, $p < 0.0001$) (Table 3). To conclude, a low BP_{TIVA} score appears to be associated with several factors linked to cerebral fragility.

3.3. Relationship between BP_{TIVA} and age

We investigate relationship between BP_{TIVA} score and patient's age, which is of particular interest since the age is not included in the score estimation. We decided to subdivide our dataset of 59 patients into three groups based on age ranges. Among the 59 patients, 18 were in the range [18, 40] years, 20 in the age group [40, 65] years and 21 were >65 years old. We took care to maintain a SEF_{95} values identical for all age subgroups during the SEF_{95} = 8–13 Hz period (where the BP_{TIVA} score was estimated). Such uniform state of hypnosis was achieved by administering to the younger population significantly higher Propofol doses compared to the elderly (4 μg/ml [3.5–4] versus 3 μg/ml [2.8–3.5], $p < 0.001$ respectively). We found that young patients had a significantly higher P_T and P_α compared to older subjects (2600 vs 980 and 463 vs 110 μV^2/Hz, $p < 0.001$ respectively). Consequently, the BP_{TIVA} score was significantly higher among young subjects compared to elderly ones (11 [9–12] versus 6 [4–7] $p < 0.001$, respectively, see Table 2). In particular, we obtained a negative correlation between the BP_{TIVA} score and age (Pearson $r = -0.78$, $p < 0.001$)

Table 3
Characteristics of population according to BP_{TIVA}.

Number of subjects	*lo*-BP_{TIVA} (n = 26)	*hi*-BP_{TIVA} (n = 33)	p
Age, median (IQR)	66.5 (60–73.25)	36 (28–53)	<0.001
Sexe, male n (%)	11 (42%)	11 (33%)	
Comorbidity			
Cardiovascular risk, n (%)	15 (58%)	9 (27%)	0.032
High blood pressure, n (%)	13 (50%)	2 (6%)	<0.001
Neurology history, n (%)	11 (42%)	19 (58%)	
Stroke, n (%)	4 (15%)	1 (3%)	
Pre-op. cognitive dysfunction, n (%)	5 (19%)	0 (0%)	0.013
Induction			
Patient with burst suppression n (%)	21 (81%)	3 (9%)	<0.001
Propofol TCI (μg/ml)	5 (5–5)	5 (5–6)	<0.001
Maintenance (SEF_{95} = 8–13 Hz)			
MAP (mmHg)	80 (75–81.25)	80 (70–80)	0.36
PSI	30.5 (29.5–32)	30 (28–32)	0.39
SEF 95 (Hz)	12 (11.8–12.125)	12.2 (11.8–12.6)	0.13
Propofol TCI (μg/ml) (range)	3 (2.8–3.375)	3.75 (3.5–4)	<0.001
Total power (μV^2/Hz)	965 (577.5–1200)	2400 (1550–3300)	<0.001
Alpha band power (μV^2/Hz)	105 (57.5–138.5)	340 (235–515)	<0.001
Total intervention			
Intervention time (min)	150 (119–210)	162 (117–198)	0.85
Propofol concentration mean (μg/ml) (range)	3.1 (2.9–3.4)	3.9 (3.57–4.1)	<0.001
Suppression time (s)	102.5 (5–338)	5 (0–64)	0.005

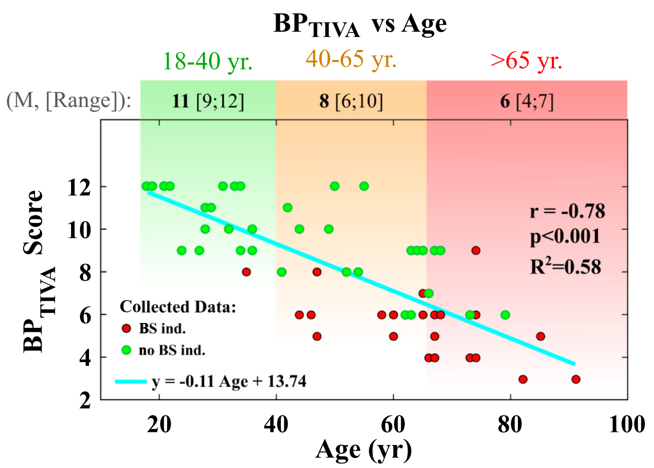

Fig. 2. Correlation between BP_{TIVA} and age for identical SEF 95 and PSI. There is a strongly negative correlation between chronological age and BP_{TIVA} (Pearson = −0.78). Interestingly, there is a wide variation in the BP_{TIVA} score for the 40–65 age group. The red dots represent patients who have had BS at induction and their BP_{TIVA} score appears to be lower than the age group standard (40–65 years). Conversely, the green dots represent patients who did not have an induction BS and their overall BP_{TIVA} is higher. BP_{TIVA} therefore seems to provide additional information and is not only strictly correlated to chronological age, especially in middle-aged patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

characterized by a linear relationship where the decreasing slope was −0.11 points/year (R^2 = 0.58, Fig. 2). Interestingly, it is shown in Fig. 3a–d four examples of spectrograms computed during SEF_{95} = 8–13 Hz for two young and two elderly patients and different BP_{TIVA} scores. We can see that young patient with a high BP_{TIVA} score had powerful alpha and delta bands (Fig. 3a) compare to older patient with low score that exhibit a weaker alpha-band (Fig. 3d). To conclude, despite not accounting for age in its calculation, the BP_{TIVA} score shows a clear linear relationship with it. However, these results illustrate that BP_{TIVA} score can assess cerebral fragility based on directly measured physiological brain properties, in this respect, it has an advantage over the age that might not always reflect specific patient fragility.

3.4. Associations BP_{TIVA} and main risk factors with BS

More frequent per-operative BS are associated with poor post-operative cognitive trajectories and thus a possible pre-existing cerebral fragility (Fritz et al., 2016; Wildes et al., 2019). We investigated how the BP_{TIVA} score was linked to occurrences of per-operative BS. During the standardized inductions of our 59 patients, 24 (41%) presented at least one BS episode (flow chart Fig. 1 and Table 4). We therefore defined two populations: patients with BS (BS_{ind} group) and patient with no BS (no BS_{ind} group) during standardized GA induction. The BP_{TIVA} score was significantly lower in the BS_{ind} group than in the no BS_{ind} group (6 [4–6] vs 10 [9–12] respectively, $p < 0.001$). Patients with BS during the induction phase were significantly older (67 vs 41 years old for patient with and without BS, respectively, $p < 0.001$), had more cardiovascular risk factors (58% with BS vs 27 % in no BS, $p = 0.032$) and had more preoperative cognitive dysfunctions (21% in BS group vs 0% in no BS, $p = 0.009$) (Table 4). Interestingly, these patients required less Propofol TCI at induction ($p = 0.046$) and had a greater MAP drop compared to those without BS (33 mmHg vs 23 mmHg, $p < 0.001$). Patient's characteristics according to presence of burst suppression are shown in Table 4. Finally, patients in BS_{ind} group spent significantly more time in burst suppression during the entire general anesthesia (166 s vs 5 s, $p < 0.001$).

3.5. Comparison between BP_{TIVA} and age in correlating with BS during induction

We used a Logistic Regression (LR) model to construct a ROC curve testing parameter association with the presence of BS during the induction. We obtained significant p-values for BP_{TIVA} and age. The BP_{TIVA} obtained the best Area Under the Curve (AUC) of 0.94 with an OR = 0.313 (Fig. 4a). We found that patients with BP_{TIVA} scores below or equal to the threshold value of 7 points had a sensitivity of 88% and a specificity of 86% to develop BS during

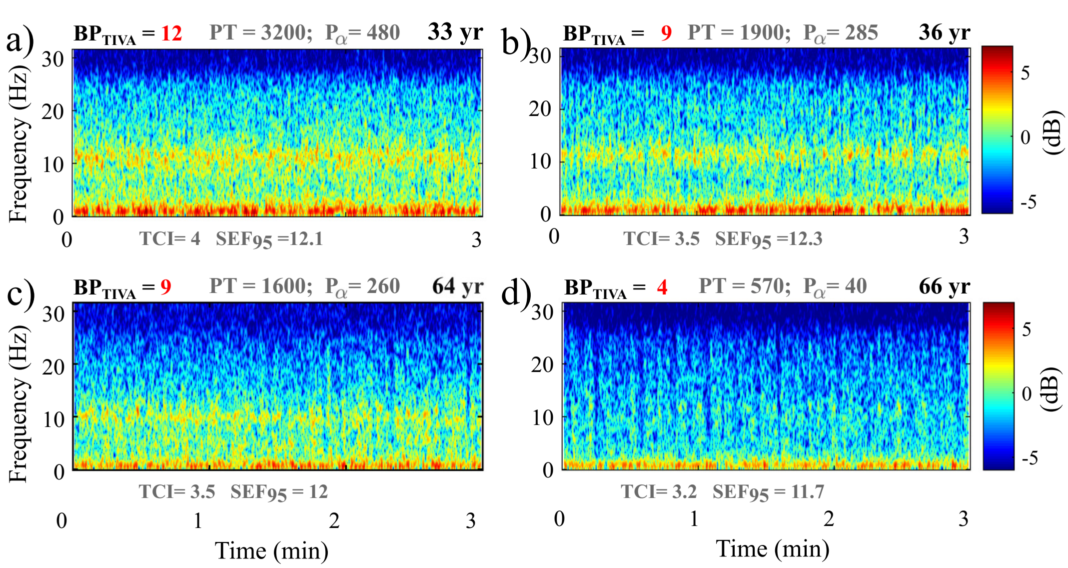

Fig. 3. Spectrogram as a function of age and BP_{TIVA} at similar SEF_{95} and PSI values. Four spectrograms with equivalent hypnosis level (SEF_{95} close to 12 Hz) of patients 33 (a), 36 (b), 64 (c) and 66 (d) years old. The corresponding BP_{TIVA} score of these 4 patients is displayed in red and the 3 parameters used to calculate the score are also noted (Propofol TCI in µg/ml, P_T and $P\alpha$ in μV^2/Hz). For the same age group, BP_{TIVA} can be very different: 12 vs 9 for (a) and (b), and 9 vs 4 for (c) and (d). Interestingly, a 36-year-old patient may have a similar spectrogram to a 64-year-old patient (b) and (c). Thus, information from the quantitative EEG and the amount of Propofol for a given level of hypnosis may therefore complementary in estimating brain fragility with chronological age. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Characteristics of population according to BS during standardized induction.

	All (=59)	Burst Suppression ($n = 24$)	No Burst Suppression ($n = 35$)	p
Age, median (IQR)	55 (34–67)	66.5 (58.5–73.75)	41 (28–63)	<0.001
Sexe, male n (%)	22 (37%)	8 (33%)	14 (40%)	0.79
Intervention				
Neuroradiology	42 (71%)	15 (63%)	27 (77%)	0.25
Orthopedic surgery	17 (29%)	9 (36%)	8 (23%)	0.13
Comorbidity				
≥1 Cardiovascular risk	24 (41%)	14 (58%)	10 (29%)	0.032
High blood pressure	14 (24%)	10 (42%)	4 (11%)	0.012
≥1 neurology history	30 (51%)	12 (50%)	18 (51%)	1
Pre-op cognitive dysfunction	5 (8%)	5 (21%)	0 (0%)	0.009
Induction				
Propofol concentration (µg/ml) median (IQR)	5 (5–5.375)	5 (4.875–5)	5 (5–6)	0.046
Delta MAP (mmHg) median (IQR)	27.5 (20–35)	32.5 (26.25–43.75)	22.5 (18.75–30)	0.002
Maintenance (SEF_{95} = 8–13 Hz)				
MAP (mmHg), median (IQR)	80 (70–80)	80 (75–80)	80 (70–80)	0.28
PSI, median (IQR)	30 (29–32)	30 (29–31.75)	30 (28–32)	0.75
SEF 95 (Hz), median (IQR)	12 (11.7–12.2)	12 (11.8–12.1)	11.9 (11.6–12.2)	0.3
Propofol concentration (µg/ml), median (IQR)	3.5 (3–3.8)	3 (2.775–3.35)	3.65 (3.5–4)	<0.001
Total power ($\mu V^2/Hz$)	1300 (980–2700)	965 (572.5–1200)	2300 (1300–3200)	<0.001
Alpha band power ($\mu V^2/Hz$)	200 (110–380)	112.5 (52.5–162.5)	325 (207–480)	<0.001
BP_{TIVA}, median (IQR)	8 (6–10)	6 (4–6)	10 (9–12)	<0.001
Total intervention				
Intervention time (min)	157 (120–200)	150 (118–220)	163 (120–200)	0.54
Suppression time (s)	10.5 (0–170.5)	166 (5–348)	5 (0–43)	<0.001

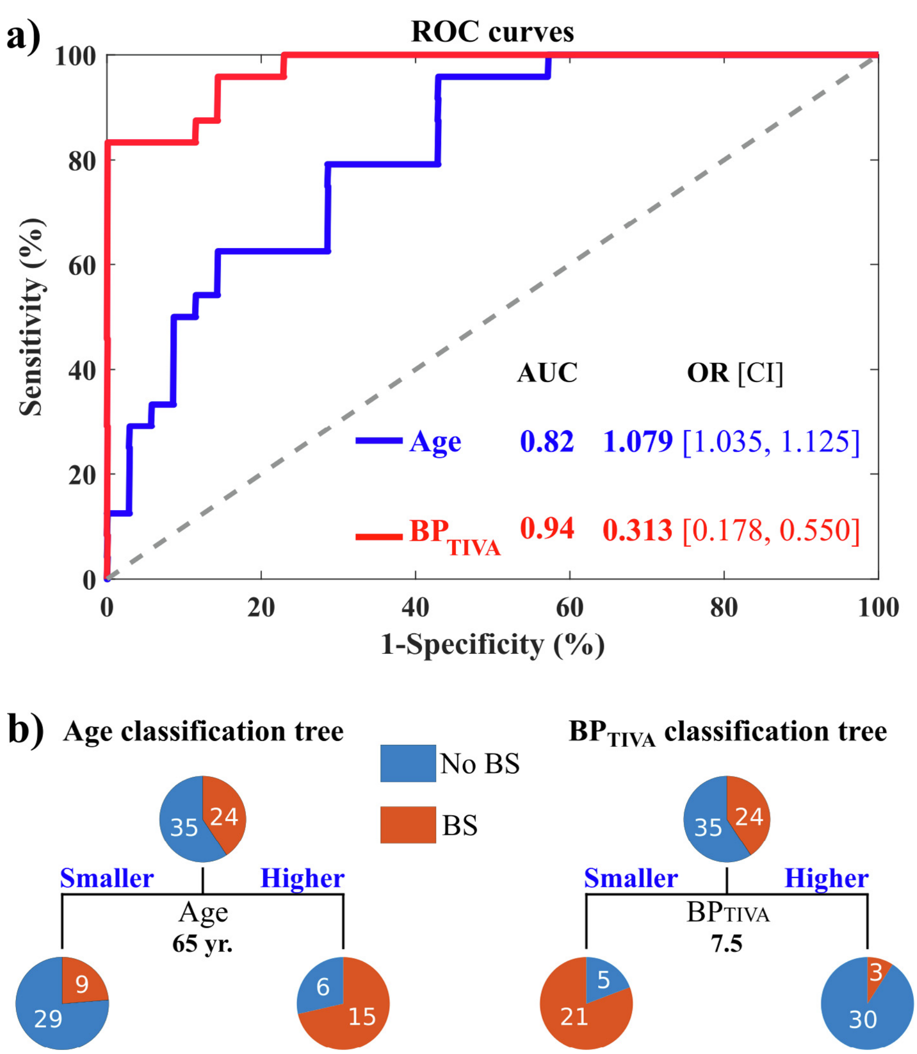

Fig. 4. Association pre-operative (age) and per-operative (BP_{TIVA}) parameters with BS at induction. (a) ROC curves and association force of age and BP_{TIVA} to BS at induction. A low BP_{TIVA} (less than or equal to 7) is strongly associated with the presence of BS at induction. This score is significantly more associated with the induction BS plot than age (AUC = 0.94 vs 0.82, $p < 0.05$). (b) Age and BP_{TIVA} classification tree for induction BS. BP_{TIVA} allows patients with early BS during standardized anesthesia to better classify, with a sensitivity and specificity of 88% and 86% vs 79% and 71% for age.

induction (Fig. 4b). In comparison, AUC computed accounting for age was 0.81 with an OR = 1.079, where an age greater than 65 years predicted BS occurrence during the induction period with a sensitivity of 78% and specificity of 71%. The AUC ROC curves for BP_{TIVA} was significantly greater than for age (AUC = 0.94 vs AUC = 0.82, $p < 0.05$). To conclude, accounting for Propofol TCI and EEG signal via the BP_{TIVA} score showed better results than the age.

4. Discussion

We found that at an equivalent level of hypnosis ($SEF_{95} \approx 12$ Hz) the EEG power spectral density was significantly lower among the elderly compared to the young patients despite a low concentration of Propofol. To quantify this finding, we have designed a score that we called BP_{TIVA}, which was strongly inversely correlated to patient's age. In addition, we observed that the BP_{TIVA} score was associated with BS occurrences by being a more important parameter than chronological age to classify patients with or without burst suppression at standardized induction. These results are of a particular interest since BS has been associated to post-operative delirium and cognitive dysfunction. The frontal EEG provided information about brain fragility as well as the propensity to develop BS pattern, assuming an adequate GA depth (SEF_{95} in the range of 8–13 Hz). Such information is still missing from most EEG monitors in the operating room, although some offer a spectral analysis over time (DSA: Density Spectral Array) which interpretation is burdensome.

Detrimental aspect of burst-suppression during the surgery still polarizes the clinical community. For some, the occurrence of burst suppression events reflect a too deep and thus harmful anesthesia, which consequences could be postoperative delirium or even permanent cognitive dysfunction (Wildes et al., 2019). Yet another interpretation consists in considering this pattern as a marker of an underlying brain fragility, existing in the patient prior surgery. Thus, per-operative BS occurrence followed by potential postoperative cognitive dysfunction would be the result of pre-existing clinical or sub-clinical brain fragility markers (Culley et al., 2017; Sprung et al., 2017; Brown et al., 2016). The first hypothesis that considers BS detrimental to the patient appears more attractive to the practitioner since it suggests the possibility to prevent or reduce postoperative cognitive dysfunction by avoiding BS periods, for instance guided by neuro-monitoring. This approach was put to the test by the recent prospective and randomized study ENGAGES (Wildes et al., 2019), where authors have demonstrated the inability to reduce POD by the lowering of per-operative burst suppression occurrences. The second hypothesis, suggesting that BS could be an epiphenomena of cerebral vulnerability, limits our capacity of action and therapeutic intervention in the operating room. At the same time, it stresses the importance to develop preventive procedures and postoperative strategies to mitigate postoperative cognitive decline.

BS events might likely become rare in the operating room. Indeed, the evolution of practices, in particular anesthetic titration of anesthetics in the elderly, leads to a reduction of per-operative BS duration. In the same way, an anesthesia guided by EEG monitoring seems to significantly reduce BS (Chan et al., 2013), the later pattern tends to be more and more avoided as neuro-monitoring in the operating room develops. Consequently, we were motivated to look for other electrophysiological characteristics predicting cognitive dysfunction, which is not associated to anesthetic overdose. This type of personalized per-operative brain fragility scores using the EEG during a stabilized period (SEF_{95}) will contribute to the development of the notion of "brain age" which is sometimes very different from chronological age.

One of the challenges in the coming years is to be able to estimate patient brain physiological age in the operating room. Indeed, per operative BS and then post-operative cognitive dysfunction (POD and POCD) appear to be linked to a set of per-operative and post-operative factors (anesthesia, surgery, inflammatory, pain, etc.) but also to pre-existing cerebral fragility that could be established before or during the surgery (Culley et al., 2017; Sprung et al., 2017; Brown et al., 2016). This cerebral fragility can be seen as a decrease in our patients' cognitive reserves and could be detected by different means before clinical symptoms appear. Inter-individual variations in brain aging potentially detected by neuropsychological tests (Mini Mental State (MMS) or the Montreal Cognitive Assessment (MoCA)) but also with bio-markers resulting from blood or cerebrospinal fluid samples or even derived from MRI, and EEG exams, all could participate in detection and prediction of cognitive trajectories and then improve post-operative medical care. In this context, the EEG quantitative analysis appears to be easy to use as well as an objective biomarker to determine the personalized physiological age of anesthetized subjects. At present, there is neither algorithm nor procedure capable of detecting specific per operative EEG markers associated with adverse post-operative neurological outcomes. By estimating the physiological age, which reflects cognitive fragility, the activity of the per-operative alpha band seems to be a good avenue for research, particularly under Propofol. Recent studies have shown that the expression of low alpha band power may be associated with peri-operative cognitive dysfunction (Kreuzer, 2017; Giattino et al., 2017). We show in our study that its low power spectral density during anesthesia is associated with an early burst suppression pattern with an even greater association when combined with total power and brain Propofol concentration (BP_{TIVA}).

This article describe a new way of using the EEG in the operating room. Here it is less a question of guiding the GA by the EEG (like BIS in 1994 and then PSI) but of detecting a probability at BS that seems to be associated with a bad cognitive evolution. The hypothesis is that the cognitive trajectory of postoperative patients is rather associated with the BP_{TIVA} score than the age or the total suppression times.

However, this study has several limitations. First, only the effect of Propofol on the EEG was investigated, nevertheless, a link between age and the decrease in power spectral density especially for the alpha band has been already demonstrated for Sevoflurane gaseous anesthetic (Purdon et al., 2015a, 2015b). In addition, age is an independent risk factor for deep hypnosis with low-dose expired sevoflurane (Sessler et al., 2012). An objective brain fragility score could therefore also be described and used under halogenated conditions. Secondly, for 23 patients, despite the instruction to maintain a SEF in the range of 8–13 Hz, the EEG signal exhibited several periods of burst suppression with no 5-min period without BS, not allowing the EEG period SEF_{13} to be obtained. It appears that for a particular subpopulation of patients, it is difficult to control and maintain an appropriate hypnosis. Such brain instability might reflect a pre-existing brain fragility. Interestingly, these patients were no older, had no more comorbidities and received on average the same doses of Propofol at induction and during the GA. However, they spent much more time in burst suppression during the entire anesthesia, including induction (see Supplementary Appendix). In these patients, a fragility score calculation will have to be adapted and BP_{TIVA} cannot be easily used. Finally, another limitation of this study is the lack of neuropsychological assessment such as MMS or MoCA. The cognitive trajectory of these patients was not specifically investigated. This objective value (BP_{TIVA}) could therefore be used and tested in the context of work on the evolution of peri operative cognitive functions.

5. Conclusion

The present paper introduces an objective score, the BP_{TIVA}, to estimate the brain physiological response to a Propofol-based TIVA. This score does not account for classical parameters such as the patient age or occurrence of burst-suppression pattern. Using a controlled period of GA where SEF_{95} was kept to 12 Hz for each patient, we show that lower BP_{TIVA} scores are associated with BS occurrences. These results suggest that monitoring alpha-band and EEG total power, accounting for Propofol doses, could objectively inform practitioner about the brain state. Therefore, integration and development of these preliminary results might as well become a tool to guide anesthesia, but above all to detect and predict brain fragility. It outlines the possibility of a tailored anesthesia, titrated and guided by neuro-monitoring technique, that would first reduce the time spent in iso-electrical suppression state, but also allows computing indexes, such as the BP_{TIVA}, to assess brain sensitivity to hypnotics. Nevertheless, although this score is related to a pre-exiting cerebral fragility, further research should go toward the exploration of associations between changes in these indexes and the incidence of post-operative cognitive complications.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.05.014.

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