Impact of impaired cerebral blood flow autoregulation on electroencephalogram signals in adults undergoing propofol anaesthesia: a pilot study

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Abstract

Background: Cerebral autoregulation actively maintains cerebral blood flow over a range of MAPs. During general anaesthesia, this mechanism may not compensate for reductions in MAP leading to brain hypoperfusion. Cerebral autoregulation can be assessed using the mean flow index derived from Doppler measurements of average blood velocity in the middle cerebral artery, but this is impractical for routine monitoring within the operating room. Here, we investigate the possibility of using the EEG as a proxy measure for a loss of cerebral autoregulation, determined by the mean flow index.

Methods: Thirty-six patients (57.5 [44.25; 66.5] yr; 38.9% women, non-emergency neuroradiology surgery) anaesthetised using propofol were prospectively studied. Continuous recordings of MAP, average blood velocity in the middle cerebral artery, EEG, and regional cerebral oxygen saturation were made. Poor cerebral autoregulation was defined as a mean flow index greater than 0.3.

Results: Eighteen patients had preserved cerebral autoregulation, and 18 had altered cerebral autoregulation. The two groups had similar ages, MAPs, and average blood velocities in the middle cerebral artery. Patients with altered cerebral autoregulation exhibited a significantly slower alpha peak frequency (9.4 [9.0, 9.9] Hz *vs* 10.5 [10.1, 10.9] Hz, $P<0.001$), which persisted after adjusting for age, norepinephrine infusion rate, and ASA class (odds ratio=0.038 [confidence interval, 0.004, 0.409]; $P=0.007$).

Conclusion: In this pilot study, we found that loss of cerebral autoregulation was associated with a slower alpha peak frequency, independent of age. This work suggests that impaired cerebral autoregulation could be monitored in the operating room using the existing EEG setup.

Clinical trial registration: NCT03769142.

Keywords: anaesthesia; brain monitoring; cerebral autoregulation; EEG; propofol; transcranial Doppler ultrasonography

Cerebral autoregulation consists of maintaining quasi-constant cerebral blood flow over a range of MAPs that vary greatly both interindividually, depending on comorbidities and the presence of acute or chronic brain injury,[1,2] and intraindividually.[3,4] Although the mechanism remains unclear, such homeostasis is critical because cerebral tissues

do not tolerate a lack of oxygen. With a small reduction in MAP, autoregulation acts on the vascular bed to maintain cerebral blood flow and prevent cellular anoxia.[5] However, this mechanism may be impaired in older individuals[6] and patients presenting with cardiovascular fragility.[7–9] During sustained hypotension, an imbalance between the oxygen supply and metabolic needs can develop and cause an increase in the oxygen extraction fraction, which may progress to brain hypoperfusion. These patients are thereafter more at risk of developing postoperative complications,[10] organ dysfunction,[11] increased mortality rates,[12] and in some cases worsening of pre-existing neurodegeneration.[13,14]

As a result, the use of generic definitions of hypotension based on blood pressure cut-offs to determine associations with adverse perioperative outcomes has recently been questioned. A new definition of hypotension based on cerebral blood flow autoregulation has emerged that allows clinicians to identify an individual's lower limit of autoregulation.[1] Real-time cerebral autoregulation monitoring offers the possibility to detect brain hypoperfusion and quickly act upon it.

Interest in cerebral autoregulation monitoring is rooted in traumatic brain injury monitoring, originally using the pressure reactivity index, which is the correlation coefficient between ICP and MAP. However, as an invasive method, it is more suited for patients with a poor neurological prognosis. The mean flow index (Mxa) represents the noninvasive counterpart of the pressure reactivity index, in which the blood velocity in the middle cerebral artery substitutes for ICP.[15,16] Although it is noninvasive, measuring the blood velocity in the middle cerebral artery using a Doppler probe poses challenges, such as steady probe-to-skin contact and frequent repositioning, making it impractical for continuous monitoring of cerebral autoregulation in the operating room.

The challenge is then to identify a proxy for the Mxa that would not depend on Doppler measurements but rather on a surrogate routinely evaluated in the operating room. A good candidate is the EEG. Inexpensive and already used for general anaesthesia monitoring, the EEG can provide features such as alpha peak frequency (α-PF) or alpha band power (α-BP) and alpha-to-slow ratio (AtS), which have all been shown to be linked to hypoperfusion states and cerebral fragility.[17–19] Several EEG patterns derived from the alpha band (8–14 Hz) have been linked to pathologies such as brain hypoperfusion after strokes[20] and delayed cerebral ischaemia in patients with a subarachnoid haemorrhage related to an aneurysm.[21] In addition, Mierau and colleagues[22] observed a slowing of the alpha band during minor cerebral ischaemia. These findings emphasise the constant neurovascular coupling linking the alpha band to the quality of cerebral perfusion and thus autoregulation. However, the link between these EEG variables and the Mxa score must be clarified.

In the present study, we investigated the feasibility of evaluating impaired cerebral autoregulation using a frontal EEG monitoring setup. We used synchronised MAP, mean flow velocity in the middle cerebral artery, and EEG signals to estimate Mxa, and then compared it with variables computed from the EEG in 36 patients under propofol-based anaesthesia. This study aims to explore the link between cerebral perfusion state and frontal EEG signals.

Methods

Ethical statement

This prospective, observational study included patients undergoing elective interventional neuroradiology procedures requiring general anaesthesia at Lariboisière Hospital (Paris, France). It was approved by the Institutional Review Board of the Société de Réanimation de Langue Française (CE SRLF 11-356). Patients were provided with an information letter, and verbal consent was obtained from each patient before anaesthesia. The study was recorded *a posteriori* on www.ClinicalTrials.gov (Clinical Trial Registration NCT03769142).

Anaesthetic protocol

General anaesthesia was induced with remifentanil followed by propofol. Remifentanil was administered using target-controlled infusion (TCI) concentrations ranging from 5 to 6 ng ml^{-1} until oral tracheal intubation and then decreased for maintenance to 2.5–3.5 ng ml^{-1}. Propofol TCI at the brain effect site started at 5 mg ml^{-1} according to the Schnider model until tracheal intubation. The anaesthesiologist could adapt the propofol TCI at any time to obtain stable anaesthesia, defined by the absence of burst suppression and a patient state index (PSI) between 25 and 35. Tracheal intubation was facilitated using atracurium (0.5 mg kg^{-1}), and the lungs were mechanically ventilated with a tidal volume of 6–8 ml kg^{-1} and a ventilatory frequency adapted to obtain an EtCO$_2$ between 35 and 38 mm Hg: the FiO$_2$ was set at 0.4. Body temperature was maintained between 36°C and 37°C. In accordance with our local protocol, a norepinephrine solution 5 μg ml^{-1} was the only vasoconstrictor used, with the infusion rate left to the discretion of the anaesthesiologist to maintain a >65 mm Hg MAP as recommended.[13]

Patient selection and data collection

Between May 2018 and July 2019, patients eligible for interventional neuroradiology surgery under general anaesthesia were selected for this prospective, observational, single-centre study. The inclusion criteria were elective surgery, planned propofol-based TIVA, and a French-speaking adult (>18 yr old) patient. Patients with the following criteria were excluded: pregnant women, history of a bleeding aneurysm (incidental finding of aneurysm during investigation of headache or tinnitus) or intracranial hypertension; emergency procedure for subarachnoid haemorrhage; and BMI >35 kg m^{-2} (for whom the Schnider pharmacokinetic model for TCI of propofol is not validated). Patient characteristics were collected during the anaesthesia consultation. The Doppler signal was measured on the side opposite the location of the aneurysm.

EEG and oximetry

Bilateral frontal EEG traces (Fp1, Fp2, F7, F8, a ground electrode Fpz, and a reference, recorded at 179 Hz) were collected from a Masimo Root® Sedline® monitor (Masimo Corporation©, Irvine, CA, USA). Frontal oximetry was performed with a Masimo Root® with O3® Regional Oximetry. The PSI, burst suppression ratio, and rSO$_2$ were transmitted to an IntelliVue MP60 monitor (Philips, Eindhoven, the Netherlands) at a

sampling rate of 125 Hz and recorded with ixTrend software (ixellence, Wildau, Germany) on a computer in .csv file format. For each patient, the EEG was exported as an .edf file from Masimo Sedline monitors using USB sticks, and then the raw traces were processed using MATLAB software, version 2018 (MathWorks Inc., Natick, MA, USA). For each patient, the recording parameters (intraoperative Masimo display setting) were kept fixed and homogeneous.[23] The EEG power spectral density was systematically computed from Fp2 electrodes.

Arterial pressure

Arterial pressure was continuously monitored, starting before anaesthesia, from the middle finger using a Clearsight® device (Edwards Lifesciences, Irvine, CA, USA). The measured analogue signal was transmitted on an IntelliVue MP60 monitor (Philips) at a sampling frequency of 125 Hz and recorded using ixTrend software (ixellence).

Transcranial Doppler

The middle cerebral artery flow velocity was recorded using a 1.5 MHz ultrasound probe placed only on one side, contralateral to the intervention site (Fig 1b). It could not remain in place during the neuroradiology procedure and was only in place during the patient's anaesthesia induction and for the subsequent 30 min. The power was set at 75 mW, the gate at 9 mm for a 45−55 mm depth, and a gain ranging from 4 to 8. The envelope of maximum velocities was acquired at a 100 Hz sampling frequency, visualised in real time using ADMS (Atys Data Management Software, Atys medical, Soucieu-en-Jarrest, FRANCE) and exported in .csv file format.

Mxa calculation

The Mxa was estimated using the methodology developed by Sorrentino and colleagues,[24] which is a Pearson's correlation coefficient computed between the averaged mean flow velocity in the middle cerebral artery and the MAP from 30 non-overlapping epochs of 10 s each (Fig 2a and b). Such time averaging removed the pulse and respiratory frequency waveforms, which are not concerned with cerebral autoregulation phenomena. Mxa was evaluated for patients with a similar and stable depth of anaesthesia of PSI between 25 and 35, without any burst suppression period, and a spectral edge frequency ranging from 8 to 15 Hz. MAP had to be greater than 65 mm Hg. In addition, during these periods, spectral edge frequency, MAP, and the infusion of propofol and remifentanil were stable (flat signals, less than 5% variation for at least 10 min). Each period had to last at least 5 min continuously. Finally, patients were separated into two groups − CA+ (Mxa <0.3) and CA− (Mxa ≥0.3) − according to the 0.3 threshold, based on previous studies conducted on patients with traumatic brain injury.[16,25]

Feature extraction from EEG traces

EEG variables were computed from the raw traces processed from concatenated .edf files. The EEG was recorded during the entire intervention. The region included for analysis had to be stable with a spectral edge frequency of 8−15 Hz. Power spectral density was computed from a Welch periodogram. Powers of the different frequency bands, including slow (0.1−1 Hz), δ (1−4 Hz), and α (8−14 Hz), were computed by averaging the power spectral density over the frequencies of interest and
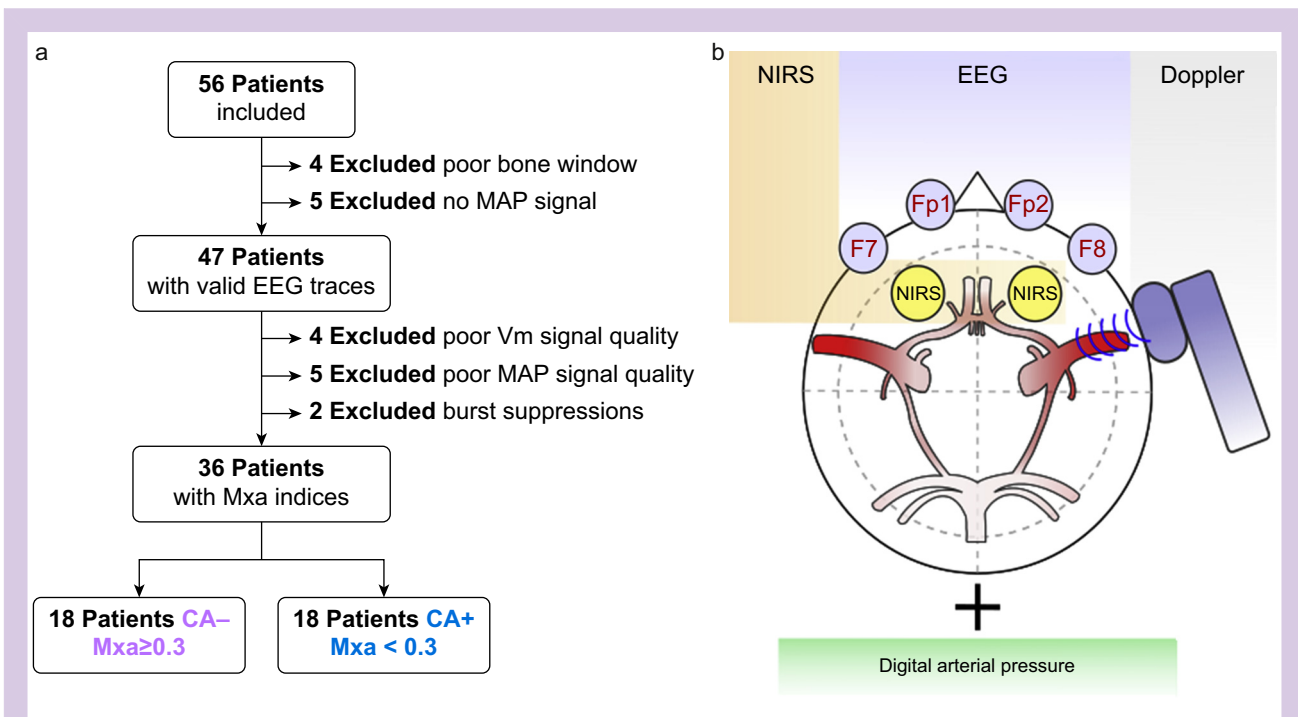

Fig 1. Patient selection, data acquisition. (a) Flowchart. (b) Schematic representation of the monitoring setup used to collect blood flow velocity (Vm) in the cerebral middle artery (Doppler), estimate perfusion (NIRS), frontal EEG traces and MAP from digital plethysmography. CA, cerebral autoregulation; Mxa, mean flow index; NIRS, near-infrared spectroscopy; Vm, mean velocity.
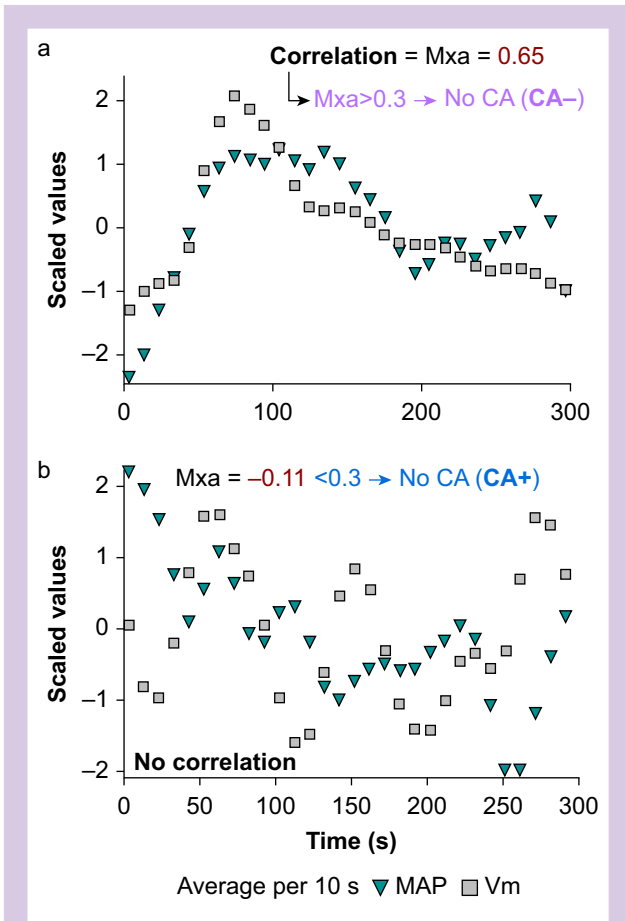
Fig 2. Mxa-based cerebral autoregulation. MAP (green diamonds) and Vm (grey squares) averaged over 10-s-long non-overlapping epochs for a patient with an impaired cerebral autoregulation CA− (upper panel, Mxa >0.3) and one with a preserved perfusion CA+ (lower panel, Mxa ≤0.3). Variables were scaled for sake of illustration. CA, cerebral autoregulation; Mxa, mean flow index; Vm, mean velocity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

presented in decibels (dB). The total power was estimated by averaging the power spectral density for frequencies from 0.1 to 25. From these powers, we derived the AtS, defined as the alpha power minus the slow power (in dB). Finally, the α-PF corresponded to the frequency estimated at which the α-BP was maximal on the power spectral density.

Statistical analysis

The significance level was α=0.05. Data with a normal distribution, assessed using the Shapiro−Wilk test, are shown as the mean (standard deviation [SD]); those with a non-normal distribution (resp. categorical variables) are expressed as the median and inter-quartile range (IQR) (resp. as the count and percentage). Covariates were compared with Fisher's *t*-test or the Mann−Whitney test as appropriate. For the multivariate analysis, only the confounding variables were imputed by the mean or the median as appropriate, whereas patients with a variable derived from the EEG alpha-band

were not included (EEG inclusion criteria). We used a multivariate logistic model to assess the effect of alpha-peak frequency of poor brain autoregulation while adjusting for confounding factors resulting from the univariate analysis. Comparison between receiver operating characteristic (ROC) areas under the curve (AUCs) computed from logistic models was performed using DeLong's test. Sample size was calculated for a statistical power of 90% using a logistic test with autoregulation as label, α-PF as the main predictor and patient age, norepinephrine, propofol, and remifentanil doses as potential confounding factors. Assuming from a preliminary analysis a P_0=0.43 probability under the null hypothesis, an odds ratio (OR) of 0.250, and an R^2 of 0.371 between main predictors and confounding factors, we enrolled 35 patients. Analyses were performed using the R-studio software (RStudio, Inc. Boston, MA, USA).

Results

Patients

In this study, 56 patients undergoing non-emergency neuroradiology surgery were prospectively included, and 36 (age: 57.5 [44.25; 66.5] yr; 38.9% women Table 1) matched stability criteria for further analysis (Fig 1a). During this period, all of the patients had a MAP of 71 (6) mm Hg, a Vm of 28 (10), and a spectral edge frequency of 13.79 (41.26) Hz (Table 2).

Comparison of high *vs* low MxA

We investigated differences in comorbidities and patient data between the CA+ (*n*=18; 50%, Mxa ≤0.3) and CA− (*n*=18; 50%, Mxa >0.3) patients (Tables 1 and 2). We found that ASA class and norepinephrine infusion rate were significantly higher among CA− patients (2 [2, 3] *vs* 2 [2, 2] points, P=0.033, and 0.06 [0.03, 0.09] *vs* 0.03 [0.02, 0.04] μg kg^{-1} min^{-1}, P=0.015, respectively; Tables 1 and 2). CA+ and CA− patients had similar ages (CA+: 53 [32, 66] yr *vs* CA− 57 [52, 65] yr; Fig 3a). Interestingly, the smallest rSO$_2$ value recorded during anaesthesia was similar between the two groups (mean [SD]: 57 [6] *vs* 50 [7]%, P=0.080, two-tailed *t*-test; Table 2).

Comparison of high *vs* low MxA: EEG

We pursued the comparison looking at different EEG markers collected during the intervention (Table 2). We found that the α-PF was slower among CA− patients (9.4 [9.0, 9.9] Hz *vs* 10.5 [10.1, 10.9] Hz, P<0.001; Figs 3d and 4a). Interestingly, there was no difference in the power of any frequency between CA+ and CA− patients (Fig 4a, Table 2). On a continuous scale, we found that Mxa and α-PF were negatively correlated (*r*= −0.556, P<0.001; Fig 4b). Patients CA+ and CA− had the same AtS (AtS: −12.55 [−13.92, −8.4] dB *vs* −13.96 [−16.13, −11.48] dB, P=0.129, Mann−Whitney test, two-tailed).

Prediction of cerebral autoregulation in anaesthetised patients

We finally evaluated whether adding an EEG marker to confounding factors could improve the detection of poor cerebral autoregulation. Using a univariate logistic linear model, we confirmed that lower α-PF was significantly associated with CA− (AUC=0.88; OR=0.069 [CI 0.013, 0.359]). We proceeded with a multivariate approach to investigate whether this effect was independent of ASA and

Table 1 Demographics and characterization of the surgical population. 'HT' HyperTension;'ASA' American Society of Anaesthesiologists. Results. α-BP, alpha band power; α-PF, alpha peak frequency; δ-BP, delta band power; PSI, patient state index; rSO_2 baseline, rSO_2 value before anaesthesia; rSO_2 min, minimal rSO_2 value; TCI, target-controlled infusion; Total P, total power; Vm, mean velocity; SEF, Spectral Edge Frequency. *Associated with a significant P-value.

Variables	All (n=36)	AC+ (n=18)	AC− (n=18)	P-value (two-tailed)
Monitored variables				
PSI	29.8 (4.5)	31.2 (5.9)	28.9 (2.9)	0.069
SEF_{95} (Hz)	13.79 (1.26)	14.00 (1.08)	13.57 (1.41)	0.306
MAP (mm Hg)	70.9 (5.7)	71.1 (5.6)	70.62 (6.0)	0.820
$EtCO_2$ (kPa)	4.27 (0.27)	4.27 (0.13)	4.40 (0.27)	0.159
Temperature	36.3 (0.4)	36.2 (0.3)	36.3 (0.4)	0.790
Propofol TCI ($\mu g\ ml^{-1}$)	3.50 [3.00, 3.50]	3.50 [3.00, 3.50]	3.50 [3.00, 3.50]	1
Remifentanil ($ng\ ml^{-1}$)	3.5 [2.5, 3.5]	3.50 [3.08, 3.58]	3.50 [3.00, 3.50]	0.819
Norepinephrine ($\mu g\ kg^{-1}\ min^{-1}$)	0.03 [0.01, 0.06]	0.03 [0.02, 0.04]	0.06 [0.03, 0.09]	0.015*
Mxa score	0.25 [0.05,0.49]	0.04 [−0.10, 0.18]	0.50 [0.38, 0.55]	<0.001*
Vm ($cm\ s^{-1}$)	28.5 (10.1)	27.33 (8.47)	29.72 (11.57)	0.485
Total P (dB)	−10.33 [−14.55, −7.65]	−8.53 [−14.57, −5.55]	−11.97 [−14.27, −9.13]	0.155
δ-BP (dB)	−3.34 [−6.73, 0.18]	−0.74 [−6.28, 1.47]	−4.66 [−6.61, −1.46]	0.206
α-BP dB)	−5.36 [−9.85, −1.25]	−2.13 [−7.89, −0.03]	−6.98 [−10.17, −2.55]	0.229
AtS (dB)	−13.37 [−15.10, −10.14]	−12.55 [−13.92, −8.41]	−13.96 [−16.13, −11.05]	0.129
α-PF (Hz)	9.95 [9.36, 10.48]	10.46 [10.10, 10.90]	9.35 [9.03, 9.82]	<0.001*
rSO_2 min (%)	54 (7.5)	57 (6)	50 (7)	0.080

norepinephrine, which were different between CA+/CA−, and from age, which could confound the effect. We found similar results as those for the univariate approach (α-PF: OR=0.038 [CI 0.004, 0.409], P=0.007). We compared the ROC AUC obtained using age, norepinephrine, and ASA with a second AUC obtained from a model using the same variables but adding α-PF. We found that adding α-PF significantly improved the prediction of poor cerebral autoregulation (AUC: 0.76 vs 0.93, P=0.017; Fig 5).

Discussion

In this study, 50% of our sample undergoing propofol anaesthesia for a neuroradiology intervention had impaired cerebral autoregulation characterised by an Mxa score greater than 0.3. Patients with impaired cerebral autoregulation had a significantly slower alpha frequency (α-PF), independent of age, ASA class, and norepinephrine infusion rate. Interestingly, ASA class and norepinephrine infusion rates were different between the two groups; CA− patients had higher ASA class and required greater vasopressor support. We did not find a significant difference in minimal rSO_2 levels during anaesthesia or in MAP. As a consequence, α-PF clearly outperformed rSO_2 in predicting higher Mxa. Furthermore, adding α-PF, an EEG variable, to age, ASA class, and norepinephrine infusion rate significantly improved the prediction of impaired autoregulation. Overall, these results suggest that alpha band slowing could reflect a loss of cerebral autoregulation and thus

Table 2 Patient details.

| Variables	All (n=36)	AC+ (n=18)	AC− (n=18)
Characteristics			
Age (yr)	57 [44, 66]	53.00 [32, 66]	57 [52, 65]
Female	14 (38.9%)	7 (38.9%)	47 (38.9%)
Height (cm)	172 (9)	171 (11)	168 (10)
Weight (kg)	70.9 (14.5)	67.8 (15.7)	74.0 (14.66)
Comorbidities			
Hypertension (%)	10 (27.8%)	3 (16.7%)	7 (38.9%)
Smoker (%)	10 (27.842.9%)	5 (27.8%)	5 (27.8%)
Diabetes (%)	4 (9.5%)	0 (0%)	4 (22.2%)
Obesity (%)	7 (19.4%)	1 (5.6%)	6 (33.3%)
ASA class	2.00 [2.00, 2.00]	2.00 [2.00, 2.00]	2.00 [2.00, 2.75]
1	3 (8.3%)	2 (11.1%)	1 (5.6%)
2	28 (77.8%)	16 (88.9%)	12 (66.7%)
3	5 (13.9%)	0 (0%)	5 (27.8%)
Type of embolisation			
Aneurysm	22 (61.1%)	10 (55.6%)	12 (66.7%)
Arteriovenous malformation	7 (19.4%)	5 (27.8%)	2 (11.1%)
Meningioma	2 (5.6%)	1 (5.6%)	1 (5.6%)
Other	5 (13.9%)	1 (5.6%)	4 (22.2%)
Intervention duration (min)	184 (67)	171.06 [50.87]	197.17 (79.04)
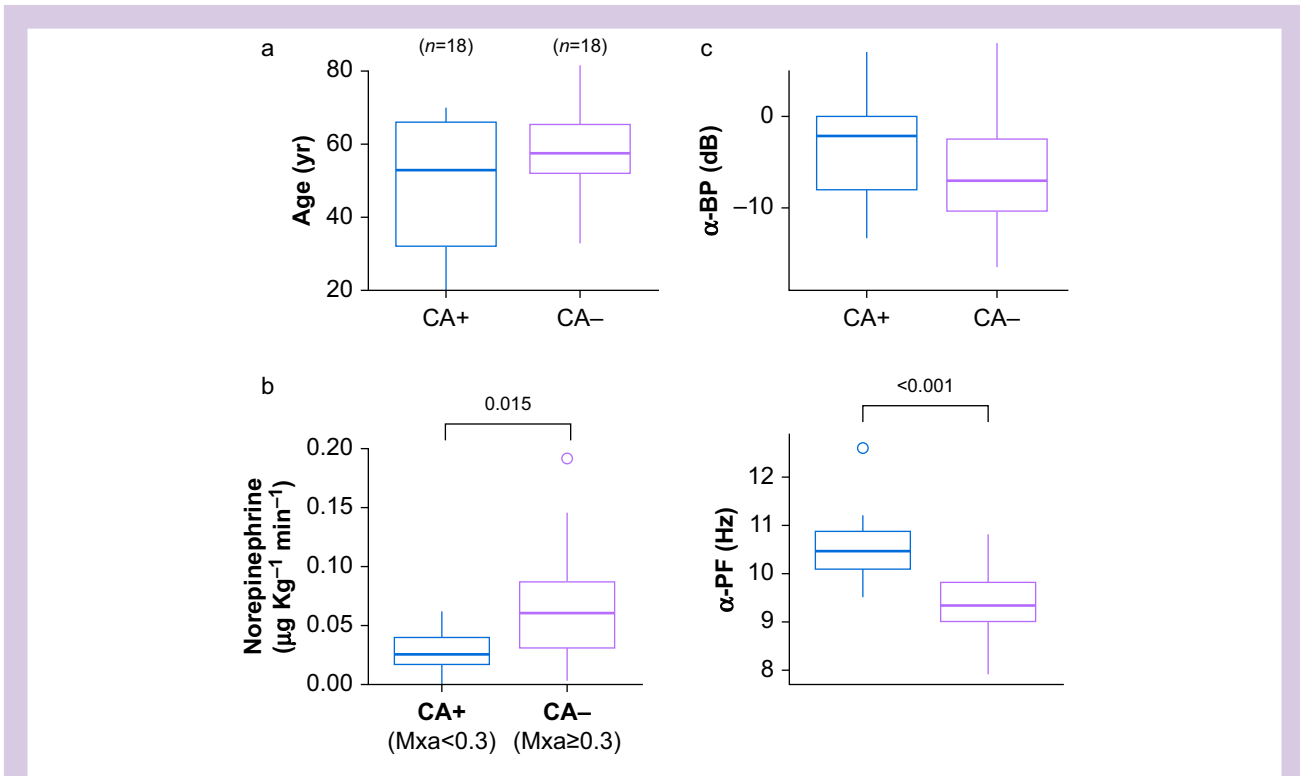
Fig 3. Box-plot. (a, b) Box-plot distributions between CA+ (blue) and CA− (purple) patients for age and norepinephrine. (c, d) Box-plot distributions between CA+ (blue) and CA− (purple) patients for α-PF, and α-BP. A significant difference between the two groups was found only for the α-PF. α-BP, alpha band power; α-PF, alpha peak frequency; CA, cerebral autoregulation; Mxa, mean flow index; Vm, mean velocity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

provide insight to improve preoperative cerebral protection using routine monitoring.

The present results emphasise the alpha band, especially its frequency, as a possible proxy actionable variable for evaluating the risk of brain hypoperfusion. These findings echo results describing changes in EEG as a result of variations in cerebral blood flow.[26] For example the EEG spectrum of patients admitted for carotid endarterectomy showed a significant increase in α-PF after the intervention, even when the stenosis was not neurologically symptomatic.[27] The correlation that we found between α-PF and Mxa, a surrogate for quality of brain perfusion, is in line with the literature. Indeed, other investigators have found a strong, positive correlation − ρ=0.68 − between the mean EEG content frequency and regional cerebral blood flow.[28] These results were obtained in healthy and awake adult subjects based on the analysis of the alpha band from occipital regions, showing similarities with those observed in the frontal areas under general anaesthesia. Nevertheless, EEG biomarkers focused on power rather than frequency have been associated with more severe pathology, such as stroke or delayed cerebral ischaemia, after cerebral haemorrhage. We could thus suggest that it is only when brain perfusion becomes more compromised, starting from the onset of ischaemia, that α-BP and then AtS decrease as well.[29,30] As general anaesthesia is a controlled environment performed here on patients without cerebral damage, the use of vasopressors is effective at avoiding severe hypoperfusion. This fact could account for our result showing changes in α-PF

but not in α-BP, in which the former might be more appropriate to detect less tractable loss of autoregulation − which is the clinical target during general anaesthesia.

The intraoperative alpha band is modulated by the depth of anaesthesia and therefore the dose of propofol. Indeed, burst suppression, a typical pattern of an anaesthetic overdose, is preceded by partial and transient suppression of the alpha band, resulting in an apparent decrease in α-BP.[19] To avoid this confounding effect, we selected EEG periods conditioned to a spectral edge frequency ranging from 8 to 15 Hz instead of setting a PSI threshold. In fact, anaesthesia depth indices, including PSI and bispectral index (BIS), are opaque algorithms, the reliability of which in monitoring fragile populations has been criticised.[31,32] For example the 2019 study by Ni and colleagues[33] showing that older people paradoxically had higher BIS values despite a high level of age-adjusted minimum alveolar concentration fractions of volatile anaesthetics, raises doubts about the reliability of this type of monitoring in older people. Conversely, navigating with spectral edge frequency allows for the identification of propofol requirements for stable anaesthesia, guaranteeing the presence of an alpha band (no burst suppression and no beta activity). The α-PF is measured during this stable period when the sedation level is neither too profound nor too light.

Characteristics of the alpha-band, including its power and frequency, are significantly tuned by age. Purdon and colleagues[34] showed that normal ageing goes hand in hand with a
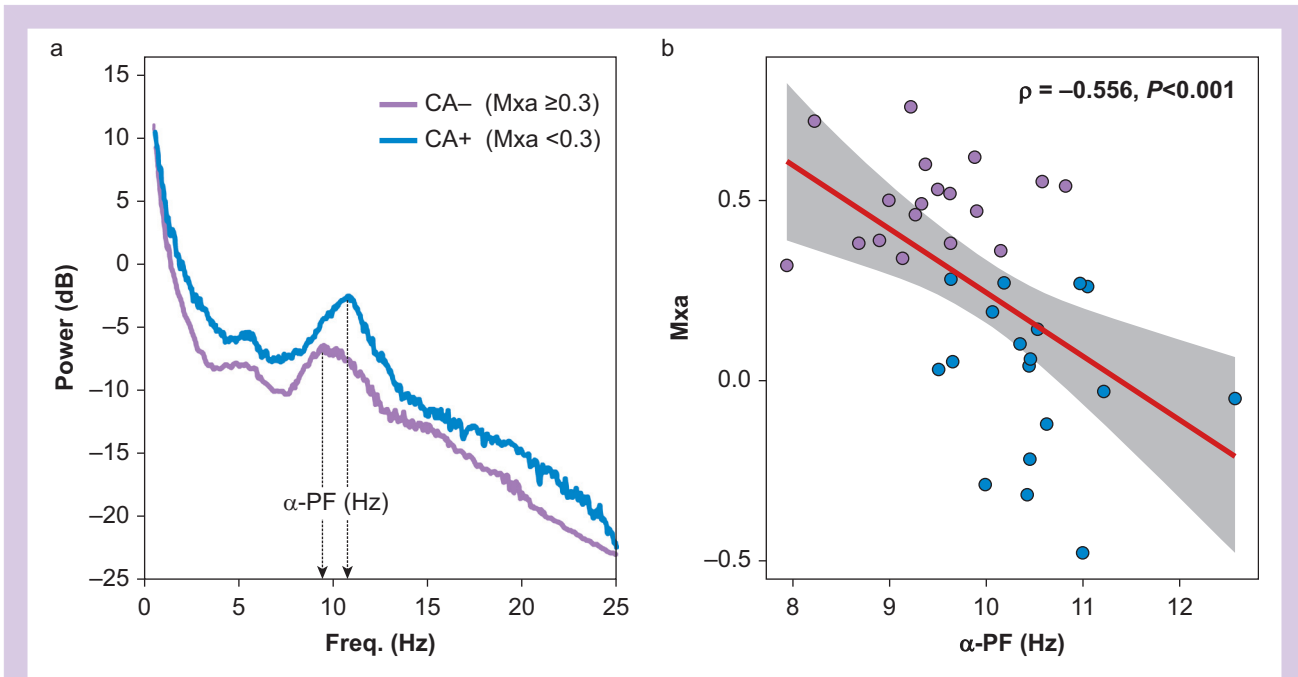
Fig 4. Alpha peak frequency slowing for patient with impaired autoregulation. (a) Averaged power spectral densities computed from EEG signals from CA+ (blue) and CA− (purple) patients. The 'bump' in the spectrum, located around 10 Hz, is characteristic of propofol-based general anaesthesia. The frequency corresponding to the maximal amplitude of this bump is the α-PF. (b) Scatterplot showing relationship between Mxa scores and the α-PF, exhibiting a significant negative correlation (red curve, $r=-0.556$, P<0.001). α-PF, alpha peak frequency; CA, cerebral autoregulation; Mxa, mean flow index. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

decrease in AtS ratio and EEG powers, especially within the range of the alpha frequency. In our study, age was similar between the two groups, and no differences in power were thus observed. Interestingly, several studies have shown that, independent of age, a weaker α-BP or discontinuous alpha but no change in α-PF was associated with cognitive decline.[35] Here, we show that impaired autoregulation is captured by the alpha frequency rather than its power, suggesting its independence from pre-existing cognitive fragility. Such compartmentalisation is reasonable because even patients with a healthy cognitive status will lose their autoregulation if the MAP decreases too much. It also suggests that tracking relative changes in α-PF during the intervention might mitigate excursions less than the lower limit of autoregulation and therefore postoperative complications.

In this study, rSO$_2$ could not be used to distinguish among patients with and without loss of cerebral autoregulation. One possible explanation could come from the clinical setup in which it was deployed. Indeed, near-infrared spectroscopy autoregulation monitoring could be leveraged to pinpoint the loss of brain autoregulation and predict postoperative complications almost exclusively among patients undergoing cardiac surgery with non-pulsatile flow. Pulsatile flow has many advantages over non-pulsatile flow, including increased haemodynamic energy leading to better blood flow to major organs, such as the brain, and maintained microcirculatory flow. As a result, Touchard and colleagues[35] demonstrated that pulsatile flow results in numerically smaller decreases in cerebral oxygen saturation levels compared with non-pulsatile flow during paediatric cardiopulmonary bypass.

Second, rSO$_2$ is an indicator of the balance between oxygen supply and oxygen demand in tissue. Such a balance is determined by a number of factors apart from cerebral blood flow, namely blood volume, metabolic rate of oxygen, capillary density, and haematocrit. Finally, contamination by extracranial tissue oxygen saturation might have played an important role,[36] particularly because of the almost systematic administration of vasoconstrictors. Thus, rSO$_2$ could simply be a result of extracranial desaturation from peripheral vasoconstriction and not a result of true cerebral desaturation.

To conclude, noncardiac surgery settings, variations in physiological factors that impact rSO$_2$, and contamination by extracranial tissue oxygen saturation might have rendered this technique less sensitive to cerebral blood flow variation and thus to the state of autoregulation assessed by Doppler. Cerebral near-infrared spectroscopy has a different goal, and it cannot truly be compared with Doppler sonography.

This study has several limitations. Although the included patients were homogeneous, the inclusion criteria and the complexity of the experimental setup led to a small number of patients and an estimated Mxa over a short time widow. A larger study is necessary to confirm the present results, particularly to clarify the respective contributions of age and other confounding factors, such as the depth of anaesthesia in the modification of alpha band properties (power/frequency). The present work is a static analysis; therefore, it is impossible to evaluate whether correcting MAP would lead to a change in α-PF for the same patient. Only a dynamic study could confirm such hypotheses. To confirm these results, a future approach could include patients with known impaired CA (e.g. patients
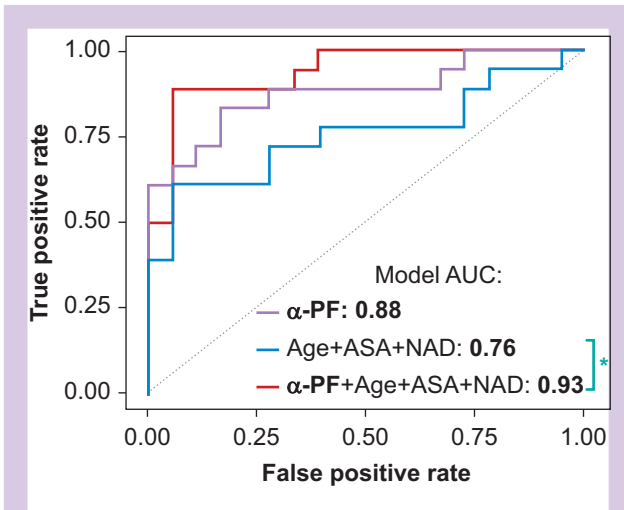
Fig 5. Predicting AC using α-PF and confounding factors. Receiver operating characteristic AUC computed from logistic model classifiers for the α-PF alone (AUC=0.88, OR=0.069 [CI 0.013, 0.359], P=0.002; lavander), Age + ASA score + NAD (AUC=0.76; blue), and all of the above (AUC=0.93, α-PF OR=0.038 [CI 0.004, 0.409], P=0.007; red). Adding α-PF to Age + ASA + NAD variables significantly improved the prediction (P=0.017, Delong test). α-PF, alpha peak frequency; AUC, area under the curve; CI, confidence interval; NAD, norepinephrine; OR, odds ratio. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

with subarachnoid haemorrhage), and a control group devoid of any neurological pathology. At the same time, an analysis of signals over longer intraoperative time windows will help to clarify the coevolution of variables, such as Vm, EEG, and rSO$_2$, particularly their behaviour/response after transient changes in MAP and the consequences for cerebral autoregulation.

Conclusions

In conclusion, we reported a significant link between intraoperative cerebral autoregulation impairment and the properties of the alpha band among patients anaesthetised for a neuroradiology procedure. This pilot study provides insights into the feasibility of assessing cerebral autoregulation during general anaesthesia based on the EEG signal, which is already routinely monitored, in contrast to the blood flow velocity, which necessitates a Doppler-based measurement. Predicting altered cerebral autoregulation in the operating room is particularly interesting as several therapeutic options exist to correct and optimise cerebral perfusion, such as the administration of norepinephrine. Developing routine monitoring for cerebral autoregulation is a challenge worth meeting to optimise intraoperative anaesthesia and mitigate postoperative complications, especially for the most fragile patients.

Authors' contributions

Study concept and design: EM, HR, FV, JM.
Acquisition of data: EM, HR, MK, CT, JS.
Interpretation of data: EM, JC, FV, JM, JJ.

Drafting of the manuscript: EM, JC.
Statistical and signal analysis: EM, JC.
Critical revision of the manuscript for important intellectual content: all authors. Final approval of the version to be published: all authors.

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