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ORIGINAL ARTICLE

Intra-operative electroencephalogram frontal alpha-band spectral analysis and postoperative delirium in cardiac surgery

A prospective cohort study

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BACKGROUND Postoperative delirium (POD) remains a frequent complication after cardiac surgery, with pre-operative cognitive status being one of the main predisposing factors. However, performing complete pre-operative neuropsychological testing is challenging. The magnitude of frontal electroencephalographic (EEG) α oscillations during general anaesthesia has been related to pre-operative cognition and could constitute a functional marker for brain vulnerability.

OBJECTIVE We hypothesised that features of intra-operative α-band activity could predict the occurrence of POD.

DESIGN Single-centre prospective observational study.

SETTING University hospital, from 15 May 2019 to 15 December 2021.

PATIENTS Adult patients undergoing elective cardiac surgery.

MAIN OUTCOME MEASURES Pre-operative cognitive status was assessed by neuropsychological tests and scored as a global *z* score. A 5-min EEG recording was obtained 30 min after induction of anaesthesia. Anaesthesia was maintained with sevoflurane. Power and peak frequency in the α-band were extracted from the frequency spectra. POD was assessed using the Confusion Assessment Method for Intensive Care Unit, the Confusion Assessment Method and a chart review.

RESULTS Sixty-five (29.5%) of 220 patients developed POD. Delirious patients were significantly older with median [IQR] ages of 74 [64 to 79] years vs. 67 [59 to 74] years; $P < 0.001$) and had lower pre-operative cognitive *z* scores (-0.52 ± 1.14 vs. 0.21 ± 0.84; $P < 0.001$). Mean α power (-14.03 ± 4.61 dB vs. -11.59 ± 3.37 dB; $P < 0.001$) and maximum α power (-11.36 ± 5.28 dB vs. -8.85 ± 3.90 dB; $P < 0.001$) were significantly lower in delirious patients. Intra-operative mean α power was significantly associated with the probability of developing POD (adjusted odds ratio, 0.88; 95% confidence interval (CI), 0.81 to 0.96; $P = 0.007$), independently of age and only whenever cognitive status was not considered.

CONCLUSION A lower intra-operative frontal α-band power is associated with a higher incidence of POD after cardiac surgery. Intra-operative measures of α power could constitute a means of identifying patients at risk of this complication.

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KEY POINTS

- Postoperative delirium remains a frequent complication after cardiac surgery.
- Pre-operative cognitive status is a leading predisposing factor for postoperative delirium.
- Intra-operative frontal EEG α-band power has been related to pre-operative cognition in previous studies.
- We demonstrated that a lower intra-operative frontal α-band power is associated with a lower cognitive score and a higher incidence of postoperative delirium.
- Measurements of intra-operative α-band power could constitute a way to identify patients at risk of postoperative delirium.

Introduction

Postoperative delirium (POD) is a frequent complication after cardiac surgery, with an incidence of 26 to 52%.[1–3] It is strongly associated with a poorer prognosis in terms of length of hospital stay, long-term cognitive impairment, and mortality.[4,5]

Advanced age is the most reported predisposing factor.[6–9] However, more important than chronological age, baseline cognitive status and the patient's ability to cope with health issues may be the leading predictive factors of POD.[10,11] Pre-operative neuropsychological testing could thus predict the risk of POD. However, performing a complete neuropsychological evaluation is time-consuming and challenging in routine practice. Therefore, other methods are needed to identify vulnerable patients.

Frontal α-band oscillations are the most prominent feature of the EEG during general anaesthesia maintained either by propofol or sevoflurane.[12,13] They are currently extensively studied as a potential biomarker of brain vulnerability, which could predict POD. α-band power decreases with age, in a more pronounced way than the other frequency bands,[14–16] and even more in the presence of underlying cognitive impairment.[17] Moreover, a lower frontal α-band power during general anaesthesia has been associated with poorer pre-operative cognitive scores,[18,19] and an increased risk of transition to a state of intra-operative burst suppression.[20,21] The latter has been correlated with POD, especially when burst suppression occurs at low anaesthetic gas concentrations.[22,23]

In this prospective study, we evaluated whether intra-operative characteristics of the spectral analysis of frontal α-band oscillations after the induction of anaesthesia are associated with the occurrence of POD in a large cohort of cardiac surgery patients. Moreover, we sought to examine whether intra-operative EEG characteristics that are associated with POD correlate with pre-operative cognitive evaluation scores. Our hypothesis was that intra-operative frontal α-band spectral analysis under general anaesthesia reflects brain vulnerability and could be a reliable and clinically feasible marker to identify patients at risk of POD in an early phase during surgery.

Methods

Population and study design

This study is part of a single-centre prospective observational project evaluating potential peri-operative predictive factors of POD. The study was approved in September 2018 by the 'Comité d'Ethique Hospitalo-Facultaire des Cliniques universitaires Saint-Luc' (B403201837550, Brussels, Belgium) and registered in ClinicalTrials.gov (NCT03706989) before starting inclusion of patients. Written informed consent was obtained from all patients, according to the Declaration of Helsinki. Enrolment started on 15 May 15 2019 and was completed on 15 December 2021.

Adult patients undergoing elective cardiac surgery through a sternotomy approach and using a normothermic cardiopulmonary bypass (CPB) were included. Surgical exclusion criteria were: emergencies, re-interventions, endocarditis, ventricular assist devices, heart transplantation, minimally invasive and robotic surgeries. Clinical exclusion criteria were: pre-operative delirium, psychiatric disorders, non-French speaking patients, pre-operative renal replacement therapy, chronic alcoholism, pre-operative liver enzyme dysfunction (liver function tests three-fold higher than the upper normal values) and use of antiepileptic medications.

Pre-operative neuropsychological testing

Two members of the research team were trained to conduct a cognitive evaluation by neuropsychologists from our Department of Neurology. The evaluation took place the day before surgery, after exclusion of pre-operative delirium using the 4AT instrument.[24] A battery of five neuropsychological tests was chosen based on the previous work of McDonagh *et al.*[25] and covered different cognitive domains: the 16-item Free and Cued Selective Reminding Test (FCSRT), the Modified Visual Reproduction Test, from the Wechsler Memory Scale, the Digit Span Test, from the revised version of the Wechsler Adult Intelligence Scale (WAIS-R), the Trail Making Test and the Digit Symbol test, from the WAIS-R.

Sample-specific z scores (individual result – mean of the studied population)/standard deviation of the studied population) were computed from five different results: the sum of the results of the three free recalls of the FCSRT, the Modified Visual Reproduction Test, the Digit Span Test, the Trail Making Test (time part B minus time part A) and the Digit Symbol Test. Ultimately, a global cognitive z score was calculated after averaging the five z scores. The final z score was used to determine the patient's pre-operative cognitive status.

Anaesthesia and cardiopulmonary bypass protocols

Standardised protocols were used for anaesthesia and CPB to limit biases regarding the risk of developing POD.

Premedication consisted of alprazolam (0.25 to 0.5 mg). In addition to standard monitoring (pulse oximetry, 12-lead ECG, invasive blood pressure and central venous pressure), a Neuro-SENSE (NeuroWave Systems Inc., Cleveland Heights, Ohio, USA) depth-of-anaesthesia monitor and a bilateral cerebral oximetry (INVOS 5100, Somanetics Corp., Michigan, USA) were routinely used. Anaesthesia was induced with midazolam (0.03 to 0.06 mg kg^{-1}), sufentanil (10 to 50 μg, titrated) and propofol, according to the raw frontal EEG and spectral analysis provided by the Neuro-SENSE monitor. Anaesthesia was maintained with sevoflurane, at a concentration guided by the Neuro-SENSE monitor (Wavelet-based Anaesthetic Value for Central Nervous System between 40 and 60, without any percentage of suppression ratio), and a continuous infusion of sufentanil (0.4 to 0.5 μg kg^{-1} h^{-1}). Repeat boluse doses of a nondepolarising muscle relaxant were used. Intra-operative administration of ketamine was not allowed. Ephedrine and/or a continuous infusion of norepinephrine were used to maintain arterial blood pressure around 60 to 70 mmHg. An intra-operative algorithm adapted from the previous work of Couture *et al.*[26] was used to optimise cerebral oxygenation and to avoid intra-operative EEG suppression episodes.

Details of the CPB protocol are available in Supplementary Material (see Supplementary Digital Content 1, http://links.lww.com/EJA/A860).

After the procedure, patients were transferred to the cardiovascular intensive care unit (ICU) with a continuous infusion of propofol (1 to 3 mg kg^{-1} h^{-1}) that was discontinued when the patient reached the criteria for mechanical ventilation weaning. Postoperative analgesia was provided by a patient-controlled analgesia pump containing either morphine or piritramide (2 mg ml^{-1}), along with paracetamol 1 g every 6 h, either intravenous or oral (for the first 2 days, then on as 'as required' basis thereafter) and, if no contraindication, ibuprofen 400 mg three times daily (for the first 2 days, then as required thereafter). If the patient was not able to take ibuprofen, intravenous ketorolac (30 mg) up to a maximum of three times a day as used instead.

Postinduction EEG recordings

Data collection

The 5 min surface EEG recordings were obtained using a 32-channel BioSemi ActiveTwo EEG recording system (BioSemi B.V., Amsterdam, The Netherlands). All the recordings were performed by a single person (CK), approximately 30 min after the induction of anaesthesia and before surgical skin incision. Exclusion of any postinduction episodes of EEG burst-suppression were systematically assessed before collecting the data. Additionally, three other intra-operative 5 min EEG recordings were included in the study protocol: after the sternotomy but before the aortic cannulation, during CPB, and after chest closure. Only the postinduction 5 min EEG recording was considered for the present study.

The electrodes were applied on the scalp following the International 10-20 System. Electrode offset was assessed before recording and optimised to below 50 μV using a low impedance high conductive gel (SignaGel, Parker Laboratories Inc., New Jersey, USA). The signal was digitised (sampling rate 2048 Hz) using a DC-coupled amplifier. Additional electrodes were placed above and lateral to the right eye, and on the right arm to assess artefacts related to eye movements and peripheral muscular activity.

EEG preprocessing

All EEG preprocessing steps were performed by a single trained person (CK), using Letswave 6 (https://www.letswave.org/), an open-source comprehensive EEG analysis toolbox for MATLAB (A. Mouraux, Institute of Neuroscience, UCLouvain, Belgium).

After linear detrending, data were re-referenced to the average of all scalp electrodes. Channels that exhibited large amplitude artefacts on a significant portion of the recording were visually identified and interpolated using the average of the three closest surrounding channels. After applying a Fast Fourier Transform (FFT) band-pass filter (0.5 to 47 Hz), the continuous EEG recordings were segmented into 5 s successive epochs. Epochs presenting signal with an amplitude greater than ±200 μV were excluded. This step was specifically used to perform an Independent Component Analysis (ICA, FastICA algorithm)[27] on the segmented data to identify independent components containing artefacts, such as cardiac or remaining muscular activity. Independent components containing such artefacts were identified visually based on their time course, frequency content and topographical distribution.

Then, a second segmentation of the continuous EEG recordings was performed. Here, each EEG epoch lasted 10 s, with an overlapping of 9 s. Spatial filtering to remove artefacts was performed using the previously obtained ICA decomposition (unmixing of the signals into independent component time courses, deletion of independent components identified as capturing artefacts, remixing of the independent component time courses into artefact-corrected EEG signals using the ICA mixing matrix). Finally, epochs containing amplitude values greater than ±200 μV were rejected.

Spectral analysis

Primary analysis A FFT with a Hanning window taper was applied to the individual preprocessed EEG epochs, leading to a spectral resolution of 0.1 Hz. Each spectrum

was finally averaged before performing data extraction. To achieve the primary objective of this study, specific attention was paid to the α-band signal recorded over frontal electrodes. Alpha frequency band was defined as the canonical range from 8 to 12 Hz. The frequency spectra from the following electrodes were averaged: Fp1, Fp2, AF3, AF4, F3, F4, F7, F8 and Fz. The following parameters of α-band activity were extracted from each individual frequency spectrum: mean α power (μV^2), maximum α power (μV^2), calculated as the mean of the 10% frequency bins exhibiting maximum power and peak α frequency (Hz) estimated as the centre of gravity frequency of α and determined using the equation:

$$f(\mathrm{CoG}) = \left[\sum_{n=f1}^{f2} \mathrm{power}(n) * \mathrm{frequency}(n)\right] / \sum_{n=f1}^{f2} \mathrm{power}(n)$$

Where f(CoG) = frequency at the centre of gravity, $f1$ = lower bound of the α-band; $f2$ = higher bound of the α-band, and n = number of samples and corresponding power values.

Secondary analyses The same parameters, mean power (μV^2), maximum power (μV^2), frequency at the centre of gravity (Hz), were extracted at the frontal channel pools for three other frequency bands canonically defined as δ [1 to 4 Hz], θ [4 to 8 Hz] and β [12 to 30 Hz]. Mean total power (μV^2) was also extracted at the same channel pools and corresponding to the range of frequencies from 0.5 to 30 Hz.

All intra-operative EEG parameters are illustrated in Fig. 1.

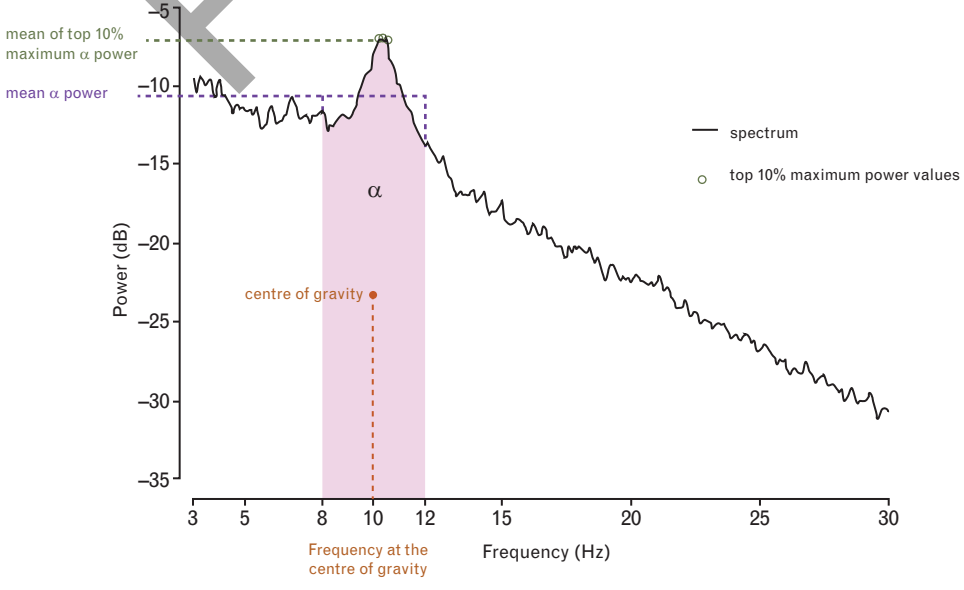
Postoperative delirium screening

Participants were screened for POD using the Confusion Assessment Method for Intensive Care Unit,[28] after tracheal tube removal and evaluation of the level of sedation by the Richmond Agitation-Sedation Scale.[29] The screening was performed by trained nurses three times a day until discharge from the ICU. On the ward, the Confusion Assessment Method was used twice a day by trained nurses until discharge from the hospital.[30] Training of the nurses was conducted by the research staff. Considering the fluctuating course of POD, a flowchart review was systematically associated with these tools to improve their accuracy.[31] The medical chart of the patients was checked by the research team for any notifications suggesting an episode of POD (e.g. aggressive or inappropriate behaviour, confusion, use of restraints, use of haloperidol, reports of hallucinations).

Statistical analysis

Our primary hypothesis was that patients presenting lower intra-operative frontal α-band power are at higher risk of POD. The sample size calculation was based on a preliminary analysis of unpublished EEG data. This analysis revealed that our cardiac surgery patients who developed POD presented lower intra-operative frontal mean α-band amplitude (0.31 μV) compared with those who did not experience POD. Putting the cut-off of low mean α-band amplitude at 0.30 μV, we observed that 36% of patients with a mean α-band amplitude less than 0.30 μV

Fig. 1 Power spectrum including the investigated EEG parameters. Alpha (α) band was canonically defined as (8 to 12 Hz). Mean α power, maximum α power (calculated as the mean of the 10% frequency bins) and frequency at α centre of gravity are the investigated parameters.



developed POD. Considering that the probability of not presenting POD would be half that in cases where the mean α-band amplitude was greater than 0.30 μV, in total, 204 patients were needed using a two-sided $\alpha = 0.05$ and a power of 80%. Taking into account any eventual dropouts, a total of 220 patients were included.

A Kolmogorov–Smirnov test was used to check the normality of data distribution. Continuous variables are presented as mean ± SD or median [IQR]. Categorical variables are presented as number (%). Comparisons of continuous variables between patients with or without POD were performed using an independent Student *t* test or a Mann–Whitney *U* test, depending on the normality assumption. A Pearson χ^2 test or a Fisher's exact test was used to compare categorical variables between the two groups.

Considering that EEG power data were not normally distributed, we converted the results in a decibel (dB) scale, using the formula:

$$\text{power(dB)} = 10 * \log \text{power}(\mu V2)$$

A univariate logistic regression analysis and a subsequent multivariate binary regression analysis assessed the influence of statistically significant variables on the occurrence of POD. A Pearson correlation coefficient was used to assess correlation between variables. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 27.

Results

The flow diagram of the study is detailed in Fig. 2. In total, 220 patients completed the study. Sixty-five patients (29.5%) experienced POD, with 34 (52.3%) of these presenting an 'hypoactive subtype', 18 (27.7%) an 'hyperactive subtype', and 13 (20.0%) a 'mixed subtype'. Patient characteristics, including comorbidities and perioperative clinical data are detailed in Table 1. Delirious patients were significantly older (74 [64 to 79] years vs. 67 [59 to 74] years; $P < 0.001$). They also had greater EuroSCORE (European System for Cardiac Operative Risk Evaluation) II scores (2.4 [1.3 to 4.0] vs. 1.5 [0.9 to 2.5]; $P < 0.001$) and a lower global cognitive *z* score (−0.52 ± 1.14 vs. 0.21 ± 0.84; $P < 0.001$). There was no significant difference regarding the surgical time and the type of surgery. Delirious patients stayed significantly longer in the ICU (3.5 ± 3 days vs. 2 ± 1 days; $P < 0.001$) and in the hospital (8 [7 to 10.5] days vs. 8 [7 to 9] days; $P = 0.006$).

Fig. 2 Flow diagram of the study.

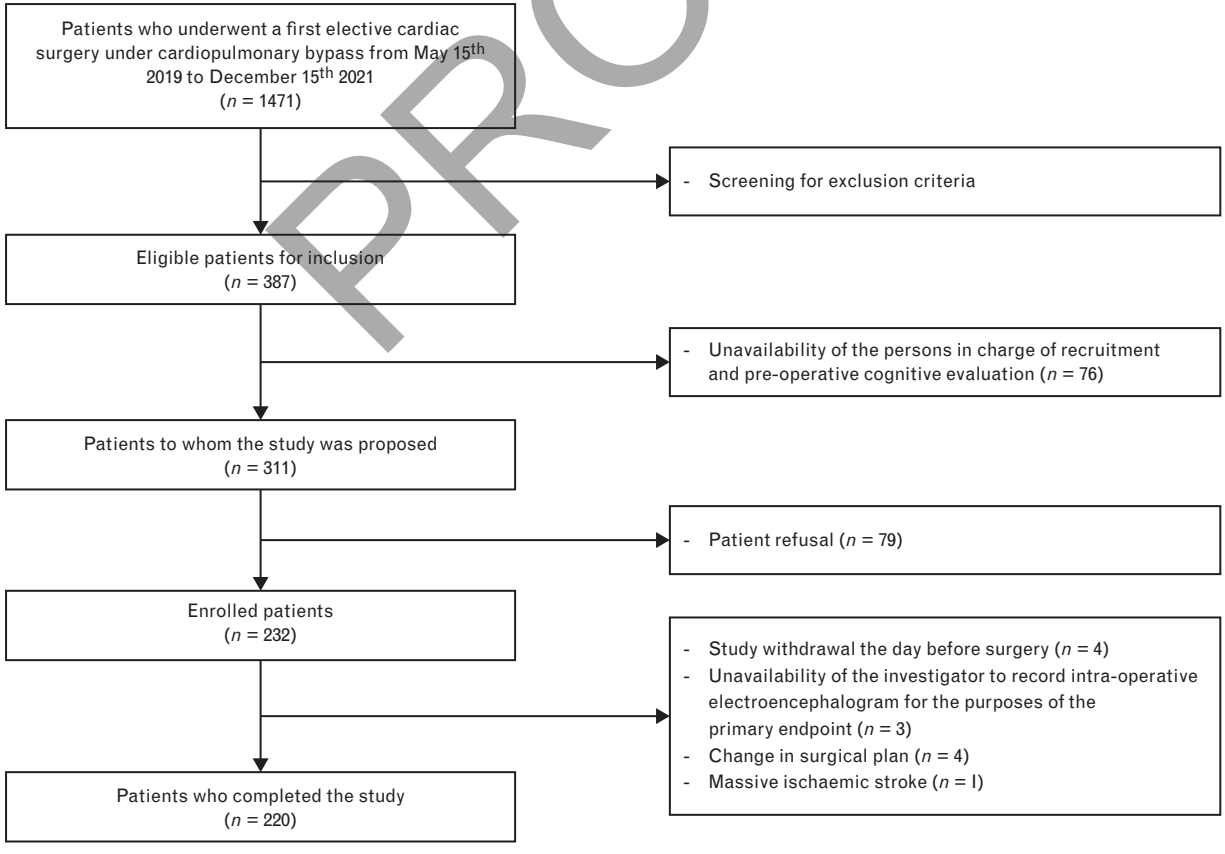


Table 1 Characteristics, comorbidities and peri-operative clinical data of patients with and without postoperative delirium

	Nondelirious patients ($n = 155$)	Delirious patients ($n = 65$)	*P*-value
Preoperative data			
Age (years)	67 [59 to 74]	74 [64 to 79]	<0.001* [a]
Sex (male)	128 (82.6)	52 (80.0)	0.651[c]
Body mass index (kg m^{-2})	27.7 [25.4 to 30.0]	28.20 [25.1 to 30.0]	0.507[a]
EuroSCORE II (%)	1.5 [0.9 to 2.5]	2.4 [1.3 to 4.0]	<0.001* [a]
Global cognitive *z* score	0.21 ± 0.84	−0.52 ± 1.14	<0.001* [b]
Hypertension	115 (74.2)	52 (80.0)	0.358[c]
Dyslipidaemia	110 (71.0)	55 (84.6)	0.033* [c]
Smoking	75 (48.4)	38 (58.5)	0.173[c]
Diabetes mellitus	41 (26.5)	21 (32.3)	0.378[c]
History of coronaropathy	23 (14.8)	12 (18.5)	0.503[c]
LVEF (%)	61 [57 to 69]	60 [53 to 66]	0.201[a]
Glomerular filtration rate (ml min^{-1})	79 [63 to 90]	70 [55 to 86]	0.016* [a]
Hb (g dl^{-1})	14.3 ± 1.4	13.7 ± 1.2	0.002* [b]
Intra-operative data			
Type of surgery			0.180[c]
Isolated CABG	74 (47.7)	26 (40)	
Single non-CABG	35 (22.6)	10 (15.4)	
2 interventions	30 (19.4)	20 (30.8)	
≥3 interventions	16 (10.3)	9 (13.8)	
Midazolam (mg)	3.0 [2.0 to 4.0]	3.0 [2.0 to 3.3]	0.943[a]
Sufentanil (μg)	190 [162 to 230]	215 [156 to 252]	0.229[a]
Propofol (mg)	80 [50 to 110]	70 [40 to 90]	0.090[a]
Surgical time (min)	226 ± 57	238 ± 60	0.170[b]
CPB time (min)	99 ± 33	112 ± 40	0.015* [b]
Aortic cross-clamp time (min)	78 ± 29	87 ± 32	0.056[b]
Nadir Hb (g dl^{-1})	9.9 ± 1.2	9.5 ± 1.2	0.013* [b]
Highest glycaemia (mg dl^{-1})	143 ± 31	152 ± 36	0.072[b]
Cell-saver (ml)	641 ± 225	642 ± 212	0.976[b]
Postoperative data			
Sedation time (h)	5.4 ± 2.5 (n = 153)	7.4 ± 5.4	0.006* [b]
Mechanical ventilation time (h)	7.3 ± 3.4 (n = 152)	9.8 ± 6.6	0.005* [b]
Peak troponin (pg ml^{-1})	736.8 ± 654.9	972.1 ± 1153.2	0.126[b]
Peak C-reactive protein (mg l^{-1})	210.9 ± 72.3	230.2 ± 69.9	0.070[b]
Opioid consumption (mg)	46 [27.5 to 73.5]	47.8 [23.2 to 65.3]	0.516[a]
Re-intervention for bleeding	8 (5.2)	4 (6.2)	0.767[c]
ICU length of stay (days)	2 ± 1	4 ± 3	0.004* [b]
Hospital length of stay (days)	8 [7 to 9]	8 [7 to 11]	0.006* [a]

Continuous variables are expressed as mean ± SD or as median [IQR]. Categorical variables are expressed as number (%). Number of patients with available data are shown in brackets. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; EuroSCORE, European system for cardiac operative risk evaluation; Hb, haemoglobin; ICU, intensive care unit; LVEF, left ventricular ejection fraction. [a] *P* values refer to group comparison by Mann–Whitney *U* test. [b] *P* values refer to group comparison by Student *t* test. [c] *P* values refer to group comparison by χ^2 test. * $P < 0.05$.

Patients who developed POD presented with significantly lower mean α power (−14.03 ± 4.61 dB vs. −11.59 ± 3.37 dB; $P < 0.001$) and lower maximum α power (−11.36 ± 5.28 dB vs. −8.85 ± 3.90 dB; $P < 0.001$) (Table 2). However, there was no statistically significant difference in terms of frequency at the α centre of gravity between the two groups. We also found similar results regarding the spectral analysis of the other frequency bands, as well as for the total power of the spectrum (Table 2). Differences in total power spectrum, mean α power and maximum α power in the frontal electrodes between patients with and without POD are illustrated in Fig. 3.

The univariate logistic regression analysis demonstrated that older age, a lower global cognitive *z* score, a lower mean α power and maximum α power and a lower mean total power were significantly associated with the occurrence of POD (Table 3).

There was a strong correlation between global cognitive *z* score and mean α power (Pearson correlation coefficient = 0.49, $P < 0.001$) and between global cognitive *z* score and maximum α power (Pearson correlation coefficient = 0.50, $P < 0.001$) (Fig. 4).

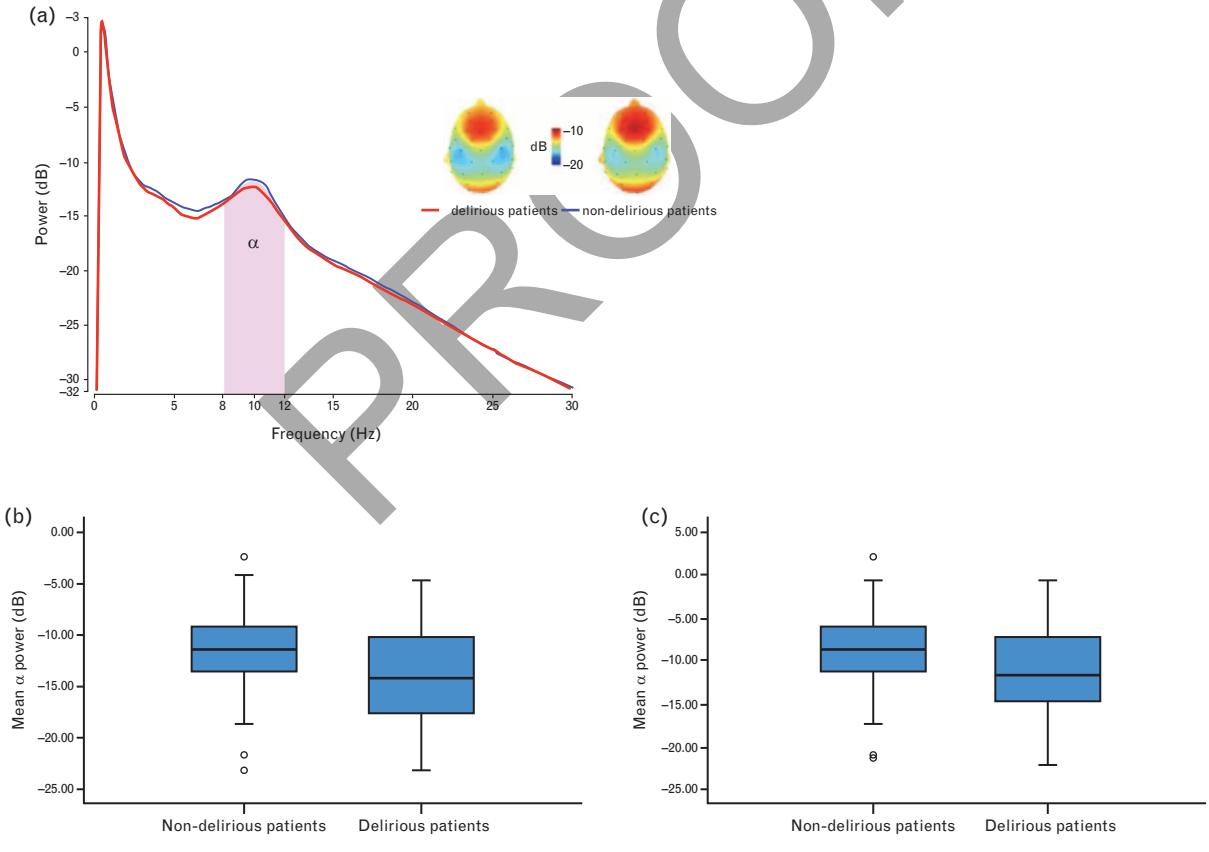
To determine whether intra-operative α-band power could represent a surrogate marker of pre-operative cognitive status, we compared four models of binary logistic regression representing different clinical situations and including age, pre-operative global cognitive *z* score and intra-operative mean α power, which all significantly influenced the occurrence of POD in our study (Table 4). To avoid multicollinearity between mean α power and maximum α power, only mean α power was integrated into the regression models. In model A, including all parameters, only the global cognitive *z* score was an independent predictive factor of POD [adjusted OR = 0.57 (95% CI, 0.387 to 0.85); $P = 0.007$]. In model B, in which patients' pre-operative cognitive status was not considered, mean α power was a significant predictive factor of POD [adjusted OR = 0.88 (95% CI, 0.81 to 0.96);

Table 2 Results of the EEG spectral analysis from the frontal region for patients with and without postoperative delirium

	Nondelirious patients ($n = 155$)	Delirious patients ($n = 65$)	*P* value
α band [8 to 12 Hz]			
Mean α power (dB)	−11.59 ± 3.37	−14.03 ± 4.61	<0.001*
Maximum α power (dB)	−8.85 ± 3.90	−11.36 ± 5.28	<0.001*
α centre of gravity (Hz)	9.92 ± 0.38	9.85 ± 0.40	0.243
δ band [1 to 4 Hz]			
Mean δ power (dB)	−8.45 ± 3.01	−9.65 ± 3.02	0.01*
Maximum δ power (dB)	−3.41 ± 3.04	−4.56 ± 3.05	0.01*
δ centre of gravity (Hz)	1.92 ± 0.13	1.89 ± 0.16	0.119
θ band [4 to 8 Hz]			
Mean θ power (dB)	−13.12 ± 3.48	−14.94 ± 3.91	0.002*
Maximum θ power (dB)	−11.55 ± 3.67	−13.37 ± 4.02	0.002*
θ centre of gravity (Hz)	5.91 ± 0.20	5.93 ± 0.19	0.420
β band [12 to 30 Hz]			
Mean β power (dB)	−21.16 ± 3.07	−23.34 ± 3.27	<0.001*
Maximum β power (dB)	−16.18 ± 3.51	−18.57 ± 3.83	<0.001*
β centre of gravity (Hz)	16.55 ± 0.76	16.84 ± 0.81	0.016*
Total spectrum [0.5 to 30 Hz]			
Mean total power (dB)	−11.68 ± 2.82	−12.77 ± 2.88	0.004*

Continuous variables are expressed as mean ± SD. *$P < 0.05$. *P* values refer to group comparison by Student *t* test.

Fig. 3 Differences in total power spectrum, mean α power and maximum α power in patients with and without postoperative delirium.



(a) Comparison of power spectra (dB) in the frequency domain between nondelirious patients (blue line) and delirious patients (red line). (b) Box plots comparing differences in mean α power (dB) between nondelirious and delirious patients. (c) Box plots comparing differences in maximum α power (dB) between nondelirious and delirious patients. Median (50th percentile) is represented by the line within the box, the bottom of the box represents the 25th percentile, the top of the box represents the 75th percentile. The whiskers represent the minimum and the maximum values within 1.5 times the height of the box, and if no case has a value outside that range, the whiskers represent the minimum or maximum values. Outliers are represented as circles above/below the whiskers lying within the range the 1.5 to 3 times height of the box.

Table 3 Univariate logistic regression analysis: dependent variable: postoperative delirium

	β (±SE)	OR (95% CI)
Age (deciles)	0.58 (±0.16)	1.79 (1.23 to 2.70)
Global cognitive *z* score	−0.78 (±0.17)	0.46 (0.333 to 0.64)
Mean α power (dB)	−0.16 (±0.04)	0.85 (0.78 to 0.92)
Maximum α power (dB)	−0.13 (±0.04)	0.88 (0.82 to 0.94)
Mean total power (dB)	−0.14 (±0.06)	0.87 (0.78 to 0.97)

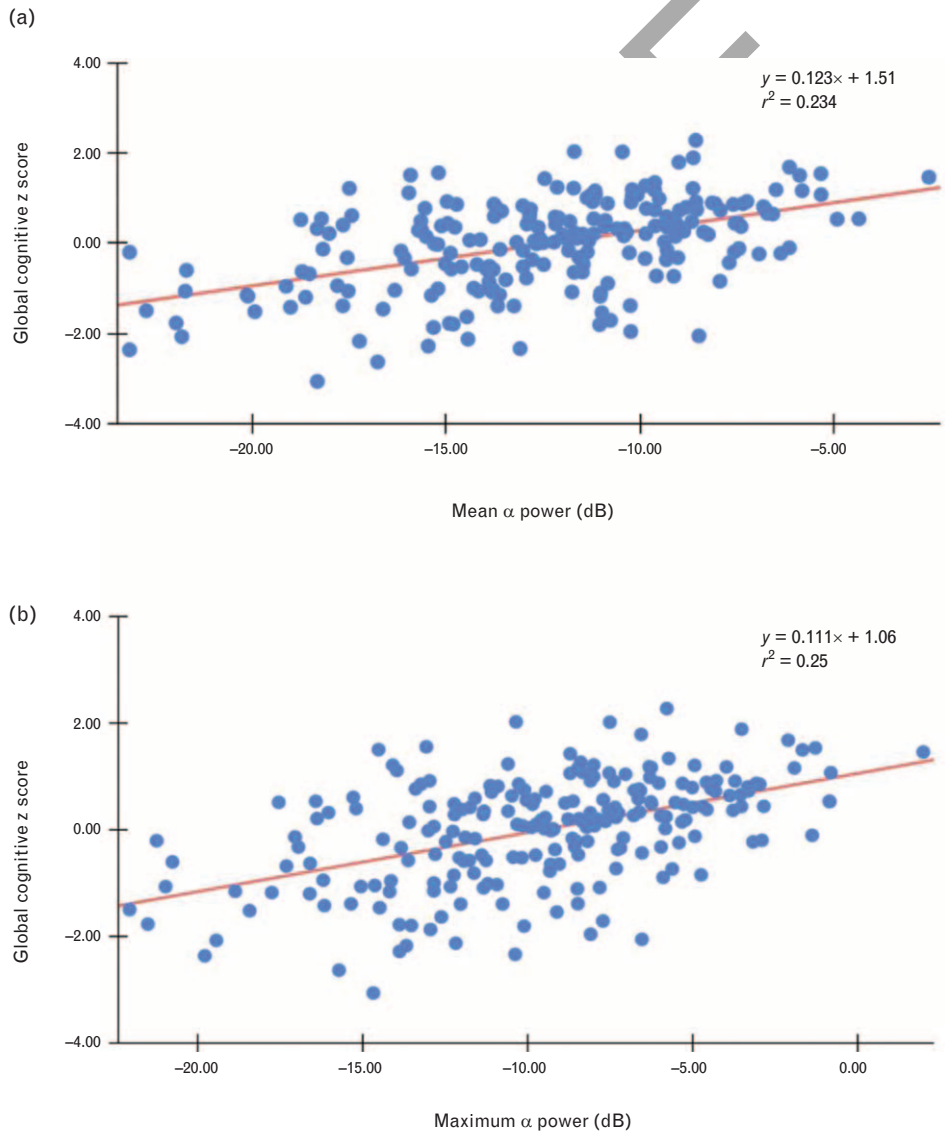
CI, confidence interval; OR, odds ratio; SE, standard error.

$P = 0.007$], independently of age. Model C demonstrated that both global cognitive *z* score and mean α power would predict POD whenever age is not included. Model D confirmed that global cognitive *z* score is a more reliable predictive marker of POD than chronological age. The sensitivity and specificity of each model were calculated and presented as Receiver Operating Characteristic curves (Fig. 5). Furthermore, we asserted the strength of mean α power as a reliable electrophysiological marker of brain vulnerability by testing the different models using mean total power instead of mean α power (see Supplementary Digital Content 2, http://links.lww.com/EJA/A861). In contrast to mean α power, mean total power did not independently predict POD when excluding pre-operative cognition or age in models B and C, respectively.

Discussion

This prospective study demonstrates that a lower α-band oscillation power under general anaesthesia is associated

Fig. 4 Correlations between pre-operative global cognitive *z* score and intra-operative mean α power and maximum α power.



(a) Correlation between global cognitive z score and mean α power (dB). (b) Correlation between global cognitive *z* score and maximum α power (dB).

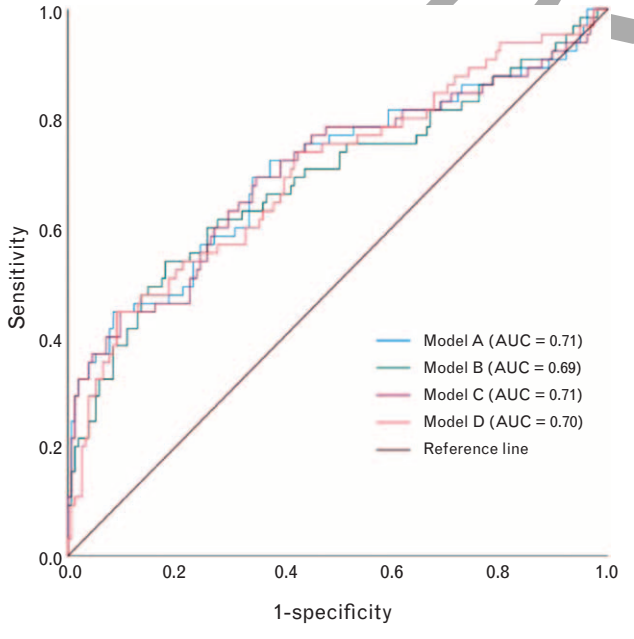
Table 4 Binary logistic regression analysis: dependent variable: postoperative delirium

	β (±SE)	Adj. OR (95% CI)
(a) Model including all the parameters		
Age (deciles)	0.09 (±0.19)	1.09 (0.75 to 1.58)
Global cognitive *z* score	−0.56 (±0.20)	0.57 (0.387 to 0.85)
Mean α power (dB)	−0.09 (±0.05)	0.91 (0.83 to 1.00)
(b) Model excluding 'Global cognitive *z* score'		
Age (deciles)	0.33 (±0.17)	1.40 (1.00 to 1.94)
Mean α power (dB)	−0.13 (±0.04)	0.88 (0.81 to 0.96)
(c) Model excluding 'Age'		
Global cognitive *z* score	−0.61 (±0.18)	0.55 (0.382 to 0.78)
Mean α power (dB)	−0.10 (±0.05)	0.91 (0.83 to 0.99)
(d) Model excluding 'mean α power'		
Age (deciles)	0.17 (±0.18)	1.18 (0.83 to 1.68)
Global cognitive *z* score	−0.68 (±0.20)	0.51 (0.347 to 0.75)

Adj. OR, adjusted odds ratio; CI, confidence interval; SE, standard error.

with a higher risk of POD. Our results are in line with those of Gutierrez *et al.*,[32] who showed that a low intra-operative α-band power during volatile general anaesthesia for major abdominal surgery was associated with an increased risk of poor scores of the Confusion Assessment Method. More recently, Koch *et al.*[33] demonstrated that a lower frontal α-band power after loss of consciousness correlated with a higher likelihood of developing POD. Alpha oscillations, in combination with slow-δ oscillations, are the main characteristics of the EEG during propofol or sevoflurane-based general anaesthesia.[12,13] This typical pattern relates to γ-aminobutyric acid receptor type A ($GABA_A$)-ergic mechanism of action. More specifically, anaesthesia-induced α oscillations are thought to reflect the synchronisation of both cortical and thalamic networks, which are responsible for unconsciousness and involves a slowing of the communication between the medial prefrontal cortex and the thalamus.[34,35] Consequently, a reduction of frontal α oscillation power during general anaesthesia might potentially attest to an impairment of this prefrontal thalamocortical feedback mechanism, probably because of a decrease in neurons implicated in the GABAergic activation[33,36] and could be an early marker of a higher risk of developing POD. In contrast to Gutierrez *et al.*,[32] we did not find any difference regarding the intra-operative frequency of α oscillations between patients who did or did not develop POD. A first reason might be our choice to assess the frequency at the centre of gravity of α oscillations rather than the peak α frequency. Indeed, a proportion of our patients exhibited split α peaks in their spectrum, making the determination of the exact peak frequency uncertain. Multiple α peaks are common characteristics of the EEG spectrum, with an incidence of approximately 44% in healthy individuals[37] and should be considered when quantifying the α rhythm. Secondly, our protocol imposed strict monitoring of depth of anaesthesia. This implied keeping every patient within an α range around 10 Hz. Consequently, the absence of difference regarding α frequency supports the hypothesis of Hight *et al.*,[36] in which the frequency of α oscillations under volatile anaesthesia preferentially reflects the depth of anaesthesia, rather than being an indicator of the underlying brain frailty. Indeed, in their study, the α frequency decreased along with increasing concentrations of anaesthetic gas agents, not α oscillation power, which probably depends on the number of neurons involved in the above-mentioned thalamocortical GABAergic mechanism.

Fig. 5 ROC curves of different models of postoperative delirium using age, preoperative global cognitive z score and intra-operative mean α power.



Model A included all the variables (age, preoperative global cognitive *z* score and mean α power). Model B included age and mean α power. Model C included preoperative global cognitive *z* score and mean α power. Model D included preoperative global cognitive *z* score and age. AUC, area under the curve.

We further demonstrated that lower pre-operative cognitive scores and lower intra-operative mean α power values were strongly associated. Associations between pre-existing cognitive impairment and intra-operative α-band power have been previously described.[18,19] We also performed a binary logistic regression analysis to evaluate whether intra-operative α-band power could be an electrophysiological marker of poorer cognitive status and thus a risk factor for POD. When considering the clinical situation in which age, pre-operative global cognitive *z* score and mean α power are known, the global cognitive *z* score was the only parameter that significantly influenced the occurrence of POD. Indeed, pre-operative cognitive impairment is a strong predisposing factor for postoperative neurocognitive disorders.[10,11] However, baseline screening of patients for cognitive impairment is not always feasible. Interestingly, we found that a model without pre-operative cognitive status but including intra-operative mean α power similarly

predicted POD, which was not the case for a model including mean total power. Moreover, a model including mean α power but without the global cognitive *z* score was actually equivalent to those models including patients' cognitive status. This finding suggests that mean α power could be an alternative to a complete pre-operative neuropsychological evaluation. It also highlights the importance of focusing on the α band, rather than the total power of the spectrum, to predict POD in this clinical context.

Additionally, we also demonstrated that intra-operative mean α power increased the probability of developing POD regardless of patient age. This emphasises the importance of considering individual brain vulnerability over chronological age.

Our secondary analyses showed that patients who experienced POD also had lower intra-operative power values in the other frequency bands and that the entire power spectrum (<30 Hz) was lower in this population. This phenomenon could be partially age-related, as delirious patients in our study were significantly older than nondelirious patients. Indeed, previous studies have described a progressive decline in the EEG power spectrum across all frequency bands with increasing age.[15,38] Further studies are needed to investigate this phenomenon as poorer pre-operative cognitive scores and more comorbidities among delirious patients in our study might also be partially responsible for this global decrease in EEG power spectrum.

A first limitation of this study is that we did not use a control group to evaluate pre-operative cognitive functions. Instead, we used the distribution of raw test scores to generate norms from the means and standard deviations of the studied population to ultimately transform these raw scores into an easily interpretable score (*z* score). Secondly, we acknowledge that there is a growing interest for 'easy-to-use' cognitive tests, such as Mini-Cog or MoCA,[39,40] which could represent alternatives to the pre-operative complete neuropsychological testing. In this perspective, future studies should evaluate the potential value of combining intra-operative frontal α-band power measures with the results of these pre-operative cognitive tests to screen patients at risk of POD. Finally, we decided to limit this study to post-induction EEG recordings. Our purpose was to find reliable predictive factors of POD as early as possible in the peri-operative period and which can be generalised to as many patients as possible. The other EEG recordings included in the study protocol will be the subject of further analyses.

Conclusion

We demonstrated that a lower intra-operative frontal Eα-band power is associated with lower cognitive scores and with a higher incidence of POD in cardiac surgery patients. We also showed that a lower intra-operative mean α power independently increased the risk of POD whenever the patient's pre-operative cognitive status is unknown. Lower intra-operative frontal α-band power might thus reflect increased brain vulnerability, itself leading to a higher risk of POD.

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Conflict of interest: VB has received funds and research support from Orion Pharma, as well as honoraria from Medtronic. He is Deputy Editor-in-Chief of the *Acta Anaesthesiologica Belgica*, and has a consultancy contract with Edwards Medical. MM is an Associate Editor of the *European Journal of Anaesthesiology* and a member of the Advisory Board of Edwards and CSL Behring. These conflicts of interest have no relationship with the presented data.

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