Journal of Clinical Monitoring and Computing (2019) 33:999–1009
https://doi.org/10.1007/s10877-019-00253-8

ORIGINAL RESEARCH

Predicting postoperative delirium and postoperative cognitive decline with combined intraoperative electroencephalogram monitoring and cerebral near-infrared spectroscopy in patients undergoing cardiac interventions

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Received: 27 October 2018 / Accepted: 3 January 2019 / Published online: 11 January 2019
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Abstract
Studies have associated electroencephalogram (EEG) suppression with postoperative delirium (POD) and postoperative cognitive decline (POCD). Otherwise, improving cerebral tissue oxygen saturation ($rScO_2$) seems beneficial. No study has evaluated the impact of EEG suppression and decreased $rScO_2$ on the incidence of POD and POCD when the intraoperative management of patients is performed with a depth-of-anesthesia (DOA) monitor and a cerebral oximetry. In this prospective study patients undergoing cardiac interventions were monitored with the NeuroSENSE® DOA monitor and bilateral cerebral oximetry. An algorithm was used to optimize cerebral oxygenation. EEG suppression was presented as total area under the curve (AUC) of suppression ratio (SR) > 0 s ($AUC_{EEGSR>0s}$). Cerebral desaturation was defined as AUC of 25% drop of oximetry values as compared to baseline. POD was evaluated by the chart review method. POCD was defined as a Z-score ≤ 2 based on Mini Mental State Examination at baseline and day 5 or if the patient reported any cognitive decline at 3 and at 6 months postoperatively. Among the 1616 patients, 1513 underwent normothermic surgery and were further analyzed. POD and POCD were respectively evaluated in 1504 and 1350 patients of whom 303 (20%) and 270 (20%) were respectively diagnosed positive. Having experienced high magnitudes of EEG suppression (fourth quartile of $AUC_{EEGSR>0s}$) was significantly associated with POD (OR = 2.247; 95% CI = 1.414–3.571; P = 0.001). Low $rScO_2$ at the end of surgery was statistically associated with POCD (OR = 0.981; 95% CI = 0.965–0.997; P = 0.018). The results of our study show that the degree of intraoperative EEG suppression on one hand, and low $rScO_2$ at the end of procedure on the other hand, are associated with respectively POD and POCD in patients undergoing cardiac interventions.

Keywords Burst suppression · Depth-of-anesthesia monitor · Cerebral oximetry · Postoperative delirium · Postoperative cognitive decline

1 Introduction

Postoperative delirium (POD) and postoperative cognitive decline (POCD) are frequent complications especially in elderly cardiac surgery patients. The incidence of POD varies between 20 and 56% after cardiac surgery [1, 2]. POD is significantly associated with increased morbidity and mortality [3, 4]. Moreover, it has been shown to be associated with POCD [5–8]. The pathophysiology of delirium in the postoperative period is not well understood [9, 10]. Many predisposing and precipitating factors have been identified resulting in POD [9]. Therefore, intraoperative measures should be taken to prevent or to reduce the incidence of POD and POCD whenever possible.

Recent studies in cardiac [11–13] and non-cardiac surgery [13–16] have suggested that avoiding excessive intraoperative anesthestic exposure and consequently electroencephalogram (EEG) suppression by using the depth-of-anesthesia

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10877-019-00253-8) contains supplementary material, which is available to authorized users.

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(DOA) monitor Bispectral Index (BIS®) decreases the incidence of POD [11–15, 17] and/or POCD [16].

On the other hand, cerebral Near-Infrared Spectroscopy (NIRS) is widely used in cardiac surgery to improve cerebral oxygenation and neurologic outcome. One randomized study showed that regional cerebral O_2 saturation ($rScO_2$) monitoring and active treatment of desaturation resulted in fewer major organ morbidity and mortality [18]. However, recent data do not yet support the usefulness of cerebral NIRS in decreasing POD and POCD [1, 19, 20].

No single study has evaluated the impact of decreased $rScO_2$ and EEG suppression on the incidence of POD and POCD when a DOA and a cerebral NIRS are simultaneously used and the intraoperative management of patients is adjusted based on the obtained information by both monitors. Moreover, no study has considered the magnitude of EEG suppression presented as area under the curve (AUC).

The primary aims of this prospective study were to determine whether the AUC of intraoperative EEG suppression detected by the DOA monitor NeuroSENSE® NS-701 (NeuroWave Systems, Inc., Cleveland, OH) and the AUC of 25% $rScO_2$ decrease as compared to the baseline values are independently associated with POD and POCD in adult patients undergoing various kinds of cardiac interventions with or without general anesthesia.

Secondarily, we assessed whether simultaneous EEG suppression and cerebral desaturation were associated with POD and POCD. We further analyzed whether any patients presented intraoperative EEG asymmetry in the presence of EEG suppression that could be indicative of an ongoing cerebral abnormality.

2 Methods

Simultaneous use of the NeuroSENSE® and bilateral cerebral oximetry is standard of care in our institution and a validated algorithm is used to optimize cerebral oxygenation whenever possible [21].

This study was performed in a tertiary hospital with a residency program. Continuous education has been provided to learn how to interpret information obtained by the cerebral oximetry monitor and especially to adapt the DOA based on the raw EEG [22]. Nevertheless, the processed EEG index was usually kept between 40 and 60. Information obtained by both monitors was combined. In case the mean arterial blood pressure was too low because of a too deep level of anesthesia as indicated by the DOA monitor, the anesthetic doses were decreased. In contrast in case the level of anesthesia was too light resulting in increased O_2 consumption and subsequent venous O_2 desaturation and thus low $rScO_2$, the anesthetic doses were increased.

Patients were eligible for the study if between 18 and 99 years. All patients undergoing first or redo cardiac surgery with or without cardiopulmonary bypass (CPB) or undergoing a transcatheter aortic valve implantation (TAVI) with or without general anesthesia or MitraClip® were included. Although the pathophysiology of neurologic complications for these interventional cardiology procedures may be different, these patients may show cerebral desaturation and EEG suppression due to hypoperfusion states. On the other hand these procedures are mostly performed under local anesthesia with or without light sedation, providing a cohort of subjects where there is no or minimal effect of anesthetic agents on intraoperative EEG. This is an important point in a trial evaluating the effect of anesthetic level on the incidence of neurologic complications.

Patients were consecutively enrolled from March 2014 until February 2017. The study finished in August 2017 as patients were contacted up to 6 months postoperatively.

Exclusion criteria were patients who could not perform the French version of Mini Mental State Examination (MMSE), patients in whom follow-up (FU) was not feasible, subjects who were preoperatively sedated and/or intubated and those who showed preoperative clinical signs of delirium.

After obtaining informed consent, a MMSE (maximum score 30) was performed and repeated at day 5 or earlier on if the patient was ready to be discharged. A FU telephone interview was realized at 3 and at 6 months postoperatively. In case the patient required a second cardiac intervention within the FU period, the latter was considered as a new intervention and the patient was followed up to 6 months after the second intervention.

2.1 Intraoperative neuromonitoring

Before induction of anesthesia, the NeuroSENSE® electrodes were placed. The NeuroSENSE® monitor uses the wavelet analysis method for the analysis of EEG activity [23, 24]. It incorporates the WAV_{CNS} (Wavelet Analysis Value for Central Nervous System monitoring) technology which is a delay-free, linear and time-invariant quantifier of cortical activity. The raw EEG signals and the processed variable WAV_{CNS} quantify brain activity in each hemisphere by using 2 bilateral channels. In contrast to other DOA monitors, the WAV_{CNS} algorithm is fully disclosed [25]. EEG suppression is presented as either the % of burst suppression ratio [(SR); low amplitude < 5 µV] or as total AUC of SR > 0 s ($AUC_{EEGSR>0s}$) presented in minutes %.

In addition to NeuroSENSE®, all patients were monitored with a bilateral cerebral oximetry (INVOS 5100; Somanetics Corporation, Troy, MI). Baseline values were obtained at room air before the induction of anesthesia. Whenever there was no possibility to place the bilateral NIRS, one single electrode was used. Cerebral desaturation was defined as

AUC of 25% drop of oximetry values as compared to the baseline ($AUC_{<25\%}$) for each hemisphere and presented as minutes%.

Combined intraoperative cerebral event was defined as $rScO_2$ decrease ($AUC_{<25\%} > 0$) for any hemisphere together with the % of SR > 0.4 for any hemisphere. The latter was chosen to exclude any eventual EEG suppression due to the anesthesia induction.

2.2 Anesthesia

Patients received a premedication whenever deemed necessary. The hemodynamic monitoring was adapted to the patient's cardiac pathology. The use of induction agents and analgesics was left at the discretion of the anesthesiologist in charge of the patient. Anesthesia was mainly maintained with sevoflurane (including during the CPB). Several anesthesiologists used a continuous infusion of propofol for the induction as well as the maintenance of anesthesia, specifically in younger patients. A continuous infusion of sufentanil was administered during the entire intraoperative period for patients undergoing cardiac surgery with CPB.

In patients undergoing a TAVI without general anesthesia, the procedure was performed under local anesthesia with or without light sedation.

2.3 Cardiopulmonary bypass

Normothermic CPB at a standardized continuous nonpulsatile flow of 2.4 l/min/m^2 was performed. The red blood cells (RBC) transfusion trigger was a hematocrit of 21% on CPB and 24% off CPB unless signs of poor tolerance or significant decrease of $rScO_2$ occurred.

2.4 Neurologic evaluation

2.4.1 Postoperative delirium

POD was evaluated during the entire hospital stay. Any sudden appearance of the following signs was assessed: altered level of consciousness in non-sedated patients, agitation and restlessness, hallucinations, disorientation in time and/or place, hyper- and/or hyporeactivity and inappropriate behavior. Delirium was assessed using the validated chart review method [26] searching in the medical record for any mention of terms that could support the diagnosis. No standard screening tests were used. The French version of the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) has been validated after the study had initiated [27].

2.4.2 Postoperative cognitive decline

POCD was defined as a Z-score ≤ 2 based on pre- and postoperative MMSE or if the patient reported any subjective complaint during the telephone interview. The following formula was used:

$$\frac{(\text{Postoperative MMSE} - \text{Preoperative MMSE}) - \text{DX MMSE normative population}}{\text{SD (DX MMSE normative population)}}.$$

The ΔX MMSE normative population is the mean value for changes in MMSE in a normative population and SD (ΔX MMSE normative population) is the standard deviation for changes in MMSE in a normative population as measured in a sample of cognitively normal population [28]. The telephone interview consisted of a questionnaire designed to evaluate the cognitive status of the patients taking into account their physical abilities which might influence the score. It was based on the Telephone Interview of Cognitive Status which is a validated score to assess the cognitive function in older adults [29]. The questionnaire used in this study (Supplemental file) was adapted for a population of patients having undergone surgery.

2.5 Statistical analysis

Statistical analyses were performed using IBM® SPSS® Statistics Version 25. In order to eliminate any bias induced by the hypothermic CPB on the EEG suppression, the data were analyzed on the cohort of the patients undergoing normothermic surgery. Indeed, the magnitude of EEG suppression would have been higher if hypothermic cases were included. This magnitude depends on the target temperature during hypothermic CPB.

All data were tested for normality. A Mann–Whitney U test and a Chi square test were used to respectively compare continuous or dichotomous variables. Data are expressed as median (Percentile 25–Percentile 75) or numbers (frequencies). A binary regression analysis was used to examine the association between EEG suppression/$rScO_2$ decrease and POD / POCD adjusting for other significant covariates.

In order to adjust for as many confounding factors as possible, we decided to perform a large study over a 3-year time period and to include approximately 1500.

For the analysis of EEG suppression only the $AUC_{EEGSR>0s}$ of the right hemisphere was used as the results were similar for the left side. For the analysis of $rScO_2$ decrease, the highest value between the right and left $AUC_{<25\%}$ was chosen (highest desaturation) to include into the regression analysis. Risk factors contributing to POD and POCD were analyzed in the univariate analysis. The variables incorporated into the multivariable model were those with a $P<0.2$ in univariate analysis.

Model fit and discrimination were evaluated using the Hosmer–Lemeshow goodness of fit test and the area under the receiver operating characteristic (ROC) curve. Absence of collinearity among the predictors was checked. As many patients did not show any EEG suppression, the $AUC_{EEGSR>0s}$ were divided into quartiles. These quartiles were treated as variables with ordinal categories in the binary regression analysis.

On the other hand as advanced age is a significant risk factor of neurologic complications, patients were divided into 4 categories of age (18–45 years; 46–60 years; 61–75 years and > 75 years). Age was treated as an ordinal variable as well.

A two-tailed $P<0.05$ was considered statistically significant.

3 Results

A total of 1616 patients were included of whom 1513 underwent surgery under normothermia (Table 1) and were further analyzed. Figure 1 shows the consort diagram.

POD occurred in 20% (303/1504) of the subjects and POCD in 20% (270/1350) of the patients. One hundred and six (7.0%) patients necessitated a new surgical intervention within the study period. Fifty-four (3.6%) patients died within the study period. No patient presented intraoperative EEG asymmetry combined with EEG suppression that could have been indicative of cerebral ischemia.

3.1 Postoperative delirium

Table 2 shows the demographic data of patients with or without POD. POD could not be evaluated in 9 patients, leaving a total of 1504 subjects to be compared. Patients suffering from POD had experienced significantly more and longer periods of EEG suppression as illustrated in Table 3. The percentage of patients with POD was significantly different ($P<0.001$; result only shown for the right hemisphere) when the total $AUC_{EEGSR>0s}$ was divided into quartiles with patients who experienced more EEG suppression showing more POD. The magnitude of cerebral oxygen desaturation was similar between patients with and without POD. However, patients with POD showed statistically significant lower $rScO_2$ values by the end of surgery. The percentage of patients receiving Scopolamine as premedication was not significantly different between patients with or without POD ($P=0.863$). The number of patients receiving midazolam, sufentanil and ketamine was not significantly different between patients with or without POD (respectively $P=0.227$; $P=0.563$; $P=0.253$). There was no significant difference between both groups with regard the administered dose of sufentanil ($P=0.833$) and the

Table 1 Characteristics and perioperative data of the normothermic cohort

Variables	n = 1513
Age (years)	68 (58–77)
Male sex	1070 (71%)
Surgery with CPB	1416 (94%)
Interventional cardiology	45 (3.0%)
EuroSCORE II	2.34 (1.25–4.05)
General anesthesia	1467 (97%)
Type of surgery	
Isolated CABG	487 (32%)
Single non CABG	509 (34%)
2 procedures	307 (20%)
3 procedures	210 (14%)
POD at ICU and/or at ward	303 (n = 1504) (20%)
POD at ICU	227 (n = 1491) (15%)
POD at ward	178 (n = 1492) (12%)
POCD	270 (n = 1350) (20%)
Postoperative stroke	22 (1.5%)
Baseline $rScO_2$ Left	62 (55–68)
Baseline $rScO_2$ Right	63 (56–69)
No postop MMSE	153 (0.1%)
Death	10
Patient refusal	17
Intubated	27
Delirium	5
Stroke	2
Not performed	89
Fatigue	3
No follow-up at 3 months	266 (18%)
Death	46
Refusal	34
No contact	186
No follow-up at 6 months	342 (23%)
Death	54
Refusal	48
No contact	240

Data are expressed as median (P25–P75) or number (%)

CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; POD, postoperative delirium; ICU, intensive care unit; POCD, postoperative cognitive decline; $rScO_2$, regional cerebral oxygen saturation; MMSE, Mini Mental State Examination

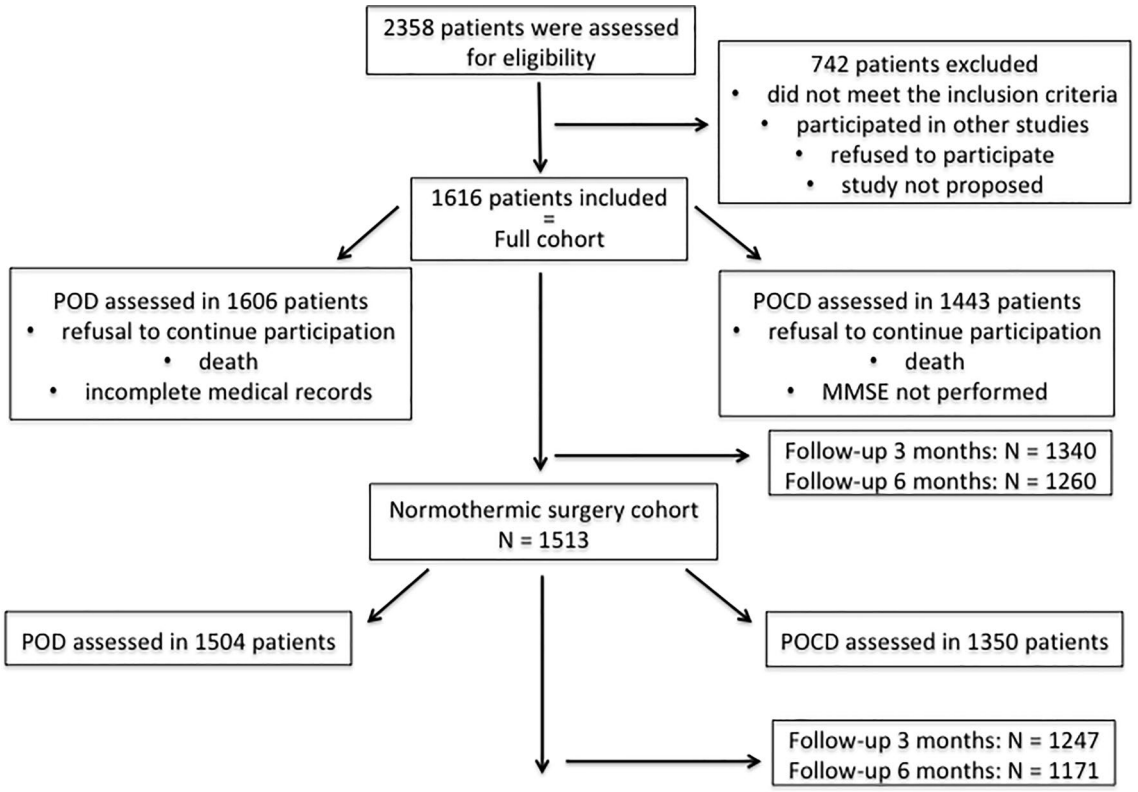

Fig. 1 Consort diagram. *POD* postoperative delirium, *POCD* postoperative cognitive decline

Table 2 Demographic data of patients with or without postoperative delirium (n = 1504) and patients with or without postoperative cognitive decline (n = 1350)

Variable	POD (n = 303)	No POD (n = 1201)	P value	POCD (n = 270)	No POCD (n = 1080)	P value
Age (years)	75 (64–80)	67 (57–75)	< 0.001	72 (61–79)	67 (57–76)	< 0.001
EuroSCORE II	2.64 (1.42–4.92)	2.25 (1.19–3.86)	0.001	2.66 (1.52–4.87)	2.16 (1.17–3.70)	< 0.001
Baseline Hb (g/dl)	13.6 (12.1–14.5)	13.9 (12.7–15.0)	0.001	13.3 (11.9–14.4)	14.0 (12.8–15.0)	< 0.001
History alcohol abuse	52 (17%)	147 (12%)	0.024	34 (1%)	114 (1%)	0.740
Lowest intraop Hb (g/dl)	8.7 (7.9–9.8)	9.2 (8.3–10.4)	< 0.001	8.7 (8.0–9.9)	9.2 (8.3–10.4)	< 0.001
Surgery with CPB	288 (95%)	1119 (93%)	0.235	253 (94%)	1024 (95%)	0.47
CPB time (min)	104 (80–136)	103 (77–132)	0.33	105 (77–133)	102 (78–131)	0.745
Interventional cardiology	6 (1.9%)	39 (3.2%)	0.247	10 (3.7%)	22 (2.0%)	0.118
General anesthesia	296 (98%)	1162 (97%)	0.317	260 (96%)	1055 (98%)	0.199
Any intraoperative transfusion	138 (46%)	381 (32%)	< 0.001	110 (41%)	338 (31%)	0.003
Intraoperative RBC transfusion	112 (37%)	286 (24%)	< 0.001	89 (33%)	252 (23%)	0.001
ICU stay (days)	3 (2–5)	2 (2–3)	< 0.001	3 (2–5)	2 (2–3)	< 0.001
Hospital stay (days)	10 (7–14)	7 (7–10)	< 0.001	9 (7–14)	7 (7–10)	< 0.001
Mortality within study period	20 (6.6%)	25 (2.1%)	< 0.001	7 (2.6%)	15 (1.4%)	0.162

Data are expressed as median (P25–P75) or number (%)

POD, postoperative delirium; POCD, postoperative cognitive decline; Hb, hemoglobin; CPB, cardiopulmonary bypass; RBC, red blood cells; ICU, intensive care unit

given dose of midazolam (P = 0.398). Patients who presented POD had received a significantly lower dose of ketamine [25 (20–35) mg] compared to those who had not shown POD [30 (20–40) mg] (P = 0.002). On the other hand a continuous infusion of propofol was used in a higher proportion of patients who did not show POD (32% vs 26%; P = 0.051).

Table 3 Neuromonitoring and neurologic data of patients with or without postoperative delirium (n = 1504) and patients with or without postoperative cognitive decline (n = 1350)

Variable	POD (n = 303)	No POD (n = 1201)	P value	POCD (n = 270)	No POCD (n = 1080)	P value
Baseline MMSE*	27 (25–29)	28 (26–29)	< 0.001	28 (26–29)	28 (26–29)	0.486
Postop MMSE*	26 (22–28)	28 (26–29)	< 0.001	23 (20–25)	28 (27–29)	< 0.001
% SR Right	2.55 (0–18.3)	1.2 (0–9.5)	< 0.001	1.95 (0–14.2)	1.3 (0–8.9)	0.02
% SR Left	2.60 (0.1–17.3)	1.2 (0–9.1)	< 0.001	1.70 (0–13.9)	1.3 (0–8.8)	0.016
$AUC_{EEGSR>0s}$ Right (min%)	367 (41–1976)	152 (6–1007)	< 0.001	242 (17–1591)	164 (8–947)	0.012
$AUC_{EEGSR>0s}$ Left (min%)	344 (40–1898)	147 (5–999)	< 0.001	245 (18–1632)	156 (6–963)	0.008
Baseline $rScO_2$ Left	60 (53–66)	62 (55–69)	0.002	60 (53–67)	62 (56–69)	0.005
Baseline $rScO_2$ Right	60 (55–67)	63 (56–69)	< 0.001	61 (54–67)	63 (57–69)	0.003
End surgery $rScO_2$ Left	62 (56–68)	64 (57–70)	0.016	62 (56–68)	64 (58–71)	0.001
End surgery $rScO_2$ Right	62 (56–70)	64 (59–71)	0.003	62 (58–67)	65 (59–72)	< 0.001
$rScO_2$ $AUC_{<25\%}$ Left	0 (0–1)	0 (0–1)	0.60	0 (0–2)	0 (0–1)	0.041
$rScO_2$ $AUC_{<25\%}$ Right	0 (0–1)	0 (0–1)	0.90	0 (0–2)	0 (0–1)	0.069
Combined intraoperative cerebral event	75 (26%) n = 289	234 (20%) n = 1152	0.037	72 (28%) n = 259	209 (20%) n = 1034	0.008
Questionnaire 3 m FU**	23 (21–24)	24 (22–25)	< 0.001	22 (20–24)	24 (22–25)	< 0.001
Questionnaire 6 m FU**	24 (22–25)	25 (23–25)	< 0.001	24 (22–25)	25 (23–25)	< 0.001

Data are expressed as median (P25–P75) or number (%)

POD, postoperative delirium; POCD, postoperative cognitive decline; MMSE, Mini Mental State Examination; SR, suppression ratio; AUC_{EEGSR}, area under curve electroencephalogram suppression ratio; $rScO_2$, regional cerebral oxygen saturation; FU, follow-up

*Maximum score = 30

**Maximum score = 25

3.2 Postoperative cognitive decline

Table 2 shows the comparison of patients with or without POCD. For various reasons shown in Table 1, there was no postoperative MMSE evaluation and no postoperative follow-up leaving in total 1350 patients to be analyzed. As shown in Table 3 patients presenting POCD had experienced more EEG suppression and showed more episodes of $rScO_2$ decline although this difference of desaturation was only significant for the left side (P = 0.041). Patients with POCD showed statistically significant lower $rScO_2$ values by the end of surgery. Significantly more patients with POCD had presented POD (33% vs 15%; P < 0.001). There was no significant difference regarding the anesthetic agents and their doses used between patients presenting POCD and those without POCD.

3.3 Predictors of POD and POCD

3.3.1 Postoperative delirium

The following variables were entered into the regression analysis: age, EuroSCORE II, baseline MMSE, history of alcohol abuse, intraoperative nadir hemoglobin, $AUC_{EEGSR>0s}$, transfusion of RBC, the mean value of the left and right $rScO_2$ at the end of surgery, combined intraoperative cerebral event, total dose of ketamine received and propofol—based anesthesia.

The model was statistically significant (P < 0.001). The Hosmer–Lemeshow test was valid ($x^2 = 2.844$; P = 0.944). Variance inflation factors (VIFs) were all < 1.5 indicating no collinearity between the independent variables. A ROC curve was created using the predicted probability of developing POD as estimated by the logistic regression analysis. The c-statistic of the curve was 0.700 [95% confidence interval (CI) 0.664–0.735; P < 0.001].

As illustrated in Table 4, having experienced high magnitudes of EEG suppression (fourth quartile of $AUC_{EEGSR>0s}$) was significantly associated with the likelihood of developing POD [odds ratio (OR) = 2.247; 95% CI for OR = 1.414–3.571; P = 0.001]. Other variables that were significantly associated with POD were age > 75 years, lower baseline MMSE and a history of alcohol abuse. Otherwise, having received a continuous infusion of propofol for the maintenace of anesthesia significantly decreased the likelihood of developing POD (OR = 0.641; 95% CI for OR = 0.454–0.906; P = 0.012).

3.3.2 Postoperative cognitive decline

The variables included in the regression analysis were: age, EuroSCORE II, $AUC_{EEGSR>0s}$, transfusion of RBC, nadir intraoperative hemoglobin concentration, mean value of the

Table 4 Predictors of postoperative delirium and postoperative cognitive decline in binary regression analysis

Variables	Odds ratio (95% CI) for POD	P	Odds ratio (95% CI) for POCD	P
EuroSCORE II (per 1% increase)	1.004 (0.974–1.035)	0.795	1.020 (0.987–1.053)	0.233
Age 18–45 years (dichotomous)	Reference variable for age		Reference variable for age	
Age 46–60 years (dichotomous)	1.489 (0.719–3.086)	0.284	1.384 (0.728–2.631)	0.322
Age 61–75 years (dichotomous)	1.647 (0.837–3.242)	0.148	1.315 (0.723–2.393)	0.369
Age > 75 years (dichotomous)	3.347 (1.688–6.637)	0.001	1.931 (1.048–3.559)	0.035
Patients with 1st quartile $AUC_{EEGSR>0s}$ (per 1 Min% increase)	Reference variable for $AUC_{EEGSR>0s}$		Reference variable for $AUC_{EEGSR>0s}$	
Patients with 2nd quartile $AUC_{EEGSR>0s}$ (per 1 Min% increase)	1.442 (0.951–2.186)	0.085	0.999 (0.667–1.498)	0.998
Patients with 3rd quartile $AUC_{EEGSR>0s}$ (per 1 Min% increase)	1.347 (0.877–2.068)	0.173	0.788 (0.515–1.206)	0.273
Patients with 4th quartile $AUC_{EEGSR>0s}$ (per 1 Min% increase)	2.247 (1.414–3.571)	0.001	1.209 (0.785–1.864)	0.389
$rScO_2$ end of surgery* (per 1% decrease)	0.996 (0.981–1.012)	0.651	0.981 (0.965–0.997)	0.018
Combined cerebral event (dichotomous)	1.024 (0.718–1.461)	0.894	1.236 (0.860–1.775)	0.252
Transfusion RBC (dichotomous)	1.136 (0.796–1.619)	0.482	1.030 (0.700–1.515)	0.880
Nadir intraoperative Hb (per 1 g/dl less)	0.981 (0.897–1.074)	0.684	0.922 (0.812–1.047)	0.213
Baseline MMSE (per 1 unit decrease)	0.887 (0.845–0.931)	< 0.001		
History alcohol abuse (dichotomous)	1.840 (1.253–2.702)	0.002		
Ketamine dose (per 1 mg increase)	0.996 (0.986–1.006)	0.438		
Propofol—based anesthesia (dichotomous)	0.641 (0.454–0.906)	0.012		
Highest value of $AUC_{<25\%}$** (per 1 Min% increase)			1.000 (0.999–1.001)	0.697
Postoperative delirium			2.340 (1.691–3.239)	< 0.001

CI, confidence interval; AUC_{EEGSR}, area under curve electroencephalogram suppression ratio; $rScO_2$, regional cerebral oxygen saturation; MMSE, Mini Mental State Examination; RBC, red blood cells; Hb, hemoglobin

*Mean value of the left and right $rScO_2$

**Highest value of cerebral oxygen desaturation (25% less compared to baseline) among the left and the right hemispheres

left and the right $rScO_2$ detected at the end of surgery, highest value of $AUC_{<25\%}$ among the left and the right hemispheres (highest cerebral oxygen desaturation), combined intraoperative cerebral event and having presented an episode of POD.

The model was statistically significant (P < 0.001). The Hosmer–Lemeshow test was valid ($x^2 = 3.217$; P = 0.920). VIFs were all < 1.3. The C-statistic was 0.66 (95% CI 0.622–0.699; P < 0.001).

As shown in Table 4, presenting an episode of POD was significantly associated with an increased odds of POCD when adjusting for other covariates (OR = 2.340; 95% CI for OR = 1.691–3.239; P < 0.001). Other independent predictors of POCD were age > 75 years and lower $rScO_2$ at the end of surgery (OR = 0.981; 95% CI for OR = 0.965–0.997; P = 0.018).

4 Discussion

In this trial POD and POCD were observed in 20% of the patients despite efforts to improve cerebral oxygenation and to titrate the anesthetic doses. We found that, in addition to several predisposing factors, high magnitude of intraoperative EEG suppression significantly increased the probability of developing POD. The latter was 124.7% [= (2.247–1) × 100%] higher for patients who belonged to the highest quartile of $AUC_{EEGSR>0s}$ than those who belonged to the lowest quartile of $AUC_{EEGSR>0s}$, holding other independent variables fixed.

Although in the multivariable analysis intraoperative EEG suppression was no longer predictive of POCD, patients who had experienced POD, had a significantly increased odds of developing POCD. On the other hand, having lower $rScO_2$ by the end of surgery was statistically associated with more POCD. However, the clinical meaning of this association is low as the corresponding OR and 95% CI are close to one. The probability of developing POCD was 1.9% [= (0.981–1) × 100%] higher if the $rScO_2$ values remained low.

This is the first large prospective study in cardiac surgery evaluating the simultaneous use of a DOA monitor and cerebral NIRS on the incidence of POD and POCD.

Our study is also the first to test this hypothesis with another DOA monitor than BIS®.

Our results are consistent with recent trials indicating that patients who experience more intraoperative EEG suppression are at increased risk of POD [11–17]. We further evaluated whether EEG suppression could put the patients at higher risk of POCD. In multivariable regression analysis the magnitude of EEG suppression was no more associated with POCD. This is in line with the study published by Radtke et al. [14]. However, others showed that avoiding too deep levels of anesthesia decreased POD as well as POCD [16]. An important finding in our study was that having experienced an episode of POD significantly put the patient at risk of POCD. These patients had significantly lower scores at the questionnaire performed at 3 and at 6 months postoperatively. This finding was also demonstrated by others [5, 6, 8]. This suggests that POD is more than just an acute fluctuating brain disorder.

In this study we sought whether the magnitude of cerebral desaturation was predictive of neurological complications. In our study the magnitude of cerebral desaturation (even when the highest desaturation was considered) did not predict POD and POCD. These results need to be interpreted with caution. All our patients received routine care which includes the use of an algorithm to avoid cerebral oxygen desaturation or to improve cerebral oxygenation. As a matter of fact we had rather few episodes of cerebral desaturation. Our interventions to improve cerebral oxygenation were thus efficacious and explain our observed results. Indeed, reversal of cerebral desaturation has been shown possible in high-risk cardiac surgery patients [30].

We found that lower $rScO_2$ values at the end of surgery were somehow associated with POCD. This is in line with other studies [31] suggesting that to decrease the incidence of POCD, higher $rScO_2$ values should be aimed. Considering that the brain undergoes physiological changes with aging [32] and that baseline $rScO_2$ may be low in specific patients [33], lower threshold of cerebral oxygen desaturation definition in our study would have probably affected our results. Indeed, cerebral desaturation was defined as a 25% decrease compared to baseline values. Many elderly and fragile patients had low baseline values and did subsequently never show any cerebral desaturation as their $rScO_2$ saturations were maintained close to baseline values. Therefore, to show whether the use of cerebral NIRS can improve the neurocognitive outcome of cardiac patients, aggressive treatment of any decline in cerebral saturation needs to be evaluated.

We further analyzed whether a combined episode of intraoperative EEG suppression and cerebral desaturation could be associated with POD and POCD but we did not find any association. EEG suppression can result from high anesthetic concentrations but also from hypoperfusion states during cardiac surgery. The incidence of combined effect has been minimized as we used an algorithm to improve $rScO_2$.

It is important to note that in this study the anesthesiologists in care of the patients were not blinded to the information obtained from both cerebral monitors. The association between EEG suppression/ $rScO_2$ decrease and POD/POCD should be tested in a double-blind randomized trial. As a matter of fact the combined use of a DOA monitor and cerebral oximetry has been shown efficacious to reduce POCD in a small randomized study in non-cardiac surgery [34] and has been recently advocated to improve the overall neurological outcome of patients [35].

The results found in our study cannot show any causal relationship between EEG suppression and POD. In many high-risk and/or elderly patients EEG suppression may occur despite low doses of anesthetics. This has been demonstrated in a recent retrospective study where patients with EEG suppression at lower volatile concentrations, showing heightened sensitivity to anesthetics, had an increased incidence of POD [36]. EEG suppression might be thus an indicator of patient's cognitive reserve. In our study low baseline MMSE was by itself an independent predictor of POD. Nevertheless, as this was not a randomized trial, it cannot be excluded that those patients with heightened sensitivity to anesthetics had received more anesthetics which resulted in increased magnitude of EEG suppression. Indeed, the correlation between EEG suppression and POD was only significant for patients belonging to the fourth quartile of EEG suppression.

We observed less POD when a continuous infusion of propofol was used. This anesthetic regimen was more often applied in younger patients ($P = 0.007$). As age > 75 years was significantly associated with an increased probability of developing POD, the choice of anesthetic agent in function of the age may have influenced these results. Several drugs such as benzodiazepines and ketamine have been reported to trigger POD. Although in this study the proportion of patients receiving these drugs was not different between those presenting POD and those without POD, any bias regarding the influence of anesthetic agents cannot be excluded. Data regarding the anesthetic regimen and POD are still conflicting and need to be studied in future trials [37–39].

We believe that the results of this study provide important information regarding the debate whether combined non-invasive cerebral monitoring should be standard of care in patients undergoing cardiac interventions.

This study has several limitations. We did not use a validated test to diagnose POD. Nevertheless the incidence of POD in our study was very similar to other trials [1, 12, 13]. In one recent trial in cardiac surgery the incidence of POD was even lower (12.5%) despite the combined use of CAM–ICU, CAM and chart review method [6].

Another limitation in our study is the diagnosis of POCD. Although MMSE is not considered as a validated test to diagnose POCD, it has been used for this purpose [5]. Cognitive changes may be very subtle in many patients and MMSE has limited ability to examine specific cognitive domains. It may not detect cognitive decline in patients with high baseline values and might be influenced by a learning effect [40]. However, we aimed to include a large number of patients and chose as such an easy test. We furthermore contacted patients up to 6 months in order to get informations regarding any subjective cognitive decline as objective tests do not always agree with the patient's self-report of cognitive status. As a matter of fact the incidence of POCD in our study was very similar to that observed by Newman et al. being 24% at 6 months [41]. We are aware that the diagnosis of POCD in our study may somehow impede comparison of our results with other trials [17, 42]. Very recently recommendations have been published for the nomenclature of cognitive change associated with anesthesia and surgery [43]. According to these recommendations the term "perioperative neurocognitive disorders" should be used which includes POD, delayed neurocognitive recovery and postoperative neurocognitive disorder. The last two terms are indicative of cognitive decline up to 30 days and 12 months after the procedure, respectively. Unfortunately, these recommendations were not available at the start of this study. Lastly, neuromonitoring was not continued in the intensive care unit.

In summary, we demonstrated that very high magnitude of intraoperative EEG suppression was significantly associated with POD. On the other hand low $rScO_2$ values by the end of surgery influenced the incidence of POCD. Furthermore POD was significantly associated with POCD. These observations occurred despite efforts to treat cerebral desaturation and to titrate anesthetics. Future trials need to investigate whether combined use of a DOA monitor and a cerebral NIRS, and aggressive treatment of any cerebral desaturation and EEG suppression lead to decreased incidence of neurologic complications in patients undergoing cardiac interventions.

Acknowledgements The authors would like to thank Prof. Zech for his advise regarding the statistical analyses.

Funding This study has received a Grant from "The Belgian Society of Anesthesiology and Reanimation" and a research Grant from "The Sorin Group". This work was supported as well by the Department of Anesthesiology of Cliniques Universitaires Saint Luc, Brussels, Belgium.

Compliance with ethical standards

Conflict of interest Mona Momeni has received speaker's fees from Medtronic. The other authors declare no conflict of interest.

Ethical approval Ethical approval for this study (2013/07NOV/508–B403201318880) was provided by Le Comité d'Ethique Hospitalo-Facultaire des Cliniques universitaires Saint Luc, Brussels, Belgium (Chairperson Prof. JM Maloteaux) on 25 November 2013. The trial was registered prior to patient enrollment at Clinicaltrials.gov (NCT02006212; Date of registration: 04/12/2013).

Informed consent Written informed consent was obtained from all subjects.

Research involving human participants This study was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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