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Original Research

Effect of Processed Electroencephalography in Cardiac Surgery: A Retrospective Analysis

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ABSTRACT

Objective: The use of brain function monitoring with processed electroencephalography (pEEG) during cardiac surgery is gaining interest for the optimization of hypnotic agent delivery during the maintenance of anesthesia. The authors sought to determine whether the routine use of pEEG-guided anesthesia is associated with a reduction of hemodynamic instability during cardiopulmonary bypass (CPB) separation and subsequently reduces vasoactive and inotropic requirements in the intensive care unit.
Design: This is a retrospective cohort study based on an existing database.
Setting: A single cardiac surgical center
Participants: Three hundred patients undergoing cardiac surgery, under CPB, between December 2013 and March 2020.
Interventions: None.
Measurements and Main Results: One hundred and fifty patients had pEEG-guided anesthesia, and 150 patients did not have a pEEG-guided anesthesia. Multiple logistic regression demonstrated that pEEG-guided anesthesia was not associated with a successful CPB separation ($p = 0.12$). However, the use of pEEG-guided anesthesia reduced by 57% the odds of being in a higher category for vasoactive inotropic score compared to patients without pEEG (odds ratio = 0.43; 95% confidence interval: 0.26-0.73; $p = 0.002$).
Conclusion: During cardiac surgery, pEEG-guided anesthesia allowed a reduction in the use of inotropic or vasoactive agents at arrival in the intensive care unit. However, it did not facilitate weaning from CPB compared to a group where pEEG was unavailable. A pEEG-guided anesthetic management could promote early vasopressor weaning after cardiac surgery.

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USE OF BRAIN FUNCTION monitoring with processed electroencephalography (pEEG) during cardiac surgery is gaining interest to optimize hypnotic agent delivery during the maintenance of anesthesia. The use of pEEG monitoring is currently not considered mandatory during cardiac surgery.[1] Closed-loop anesthesia using the bispectral index (BIS) has been shown to decrease propofol administration and to increase hemodynamic stability during surgery.[2] BIS monitoring has been associated with reductions in either propofol or isoflurane administration for patients undergoing both on-pump and off-pump cardiac surgeries.[3-5] Indeed, unnecessary high doses of anesthetic agents can induce systemic vasodilatation and hypotension and therefore increase the need for inotropic and vasoactive agents during surgery.[6-8] Therefore, pEEG-guided anesthesia may reduce the use of vasoactive and inotropic agents after the surgery by improving hemodynamic stability at the end of the procedure. It's well documented that high doses of vasoactive and inotropic drugs in the postoperative period are a good predictor of mortality and renal dysfunction.[9,10]

There is relatively little evidence regarding the use of pEEG and a reduction in vasopressors and inotrope use during surgical procedures.[11,12] According to the recent Engages randomized clinical trial, patients with pEEG-guided anesthesia seem to receive lower quantities of phenylephrine, epinephrine, ephedrine, and milrinone during major non-cardiac surgery.[12] Statistical analysis was not performed on these data. Moreover, one team has shown that BIS-guided titration of sevoflurane during cardiac surgery using cardiopulmonary bypass (CPB) decreases the mean cumulative dose of norepinephrine administration compared to a control group.[11]

There are actually no studies examining the impact of pEEG-guided anesthesia on weaning from CPB and vasoactive and inotropic requirements postoperatively in the intensive care unit (ICU) after cardiac surgery. It is hypothesized that adapting the dose of anesthetic agents of pEEG-guided anesthesia during cardiac surgery will decrease the use of inotropes to achieve successful CPB separation. Secondarily, this study hypothesizes that pEEG-guided anesthesia will reduce postoperative inotropic and vasoactive drug requirements in the ICU as measured by the vasoactive-inotropic score (VIS).

Methods

Setting and Study Population

After approval from the institutional research and ethics committee, a retrospective single-center cohort study was designed. The transesophageal echocardiographic database[13,14] contains consecutive cardiac surgery patients performed under the supervision of 1 anesthesiologist. For this study, 2 independent investigators screened this database and the electronic patient record research registry database (Compurecord Peri-Operative System Version G.01 2015; Philips Healthcare, The Netherlands) for consecutive patients undergoing cardiac surgery using CPB between December 2013 and March 2020. Patients were distributed into 2 groups depending on whether anesthesia was guided by pEEG or not. Patients in the pEEG-guided anesthesia group were selected after the implementation of pEEG monitoring in a tertiary care hospital as the institutional standard practice in 2017. Patients in the control group corresponded to patients who underwent cardiac surgery prior to the implementation of pEEG monitoring as standard practice. Only adult patients undergoing cardiac surgery with the use of CPB were included. Patients undergoing a heart transplant and left ventricular assist device insertion were excluded. For patients in the treatment group, the SedLine (Masimo Corporation, Irvine, CA) pEEG was used. Anesthetic induction included midazolam or propofol, and fentanyl tracheal intubation was facilitated with rocuronium, after which the maintenance of anesthesia was performed with a combination of isoflurane or sevoflurane, fentanyl, and propofol. The use of vasoactive agents was systematized based on a previously described and validated algorithm for intraoperative vasoactive management.[15-17] Postoperative management and timing of extubation were performed according to the institutional protocol and under direct supervision of an intensivist. Intraoperative patients' management was the same between the 2 groups.

The primary goal was to determine if pEEG-guided anesthesia was associated with a reduced rate of hemodynamic instability during CPB separation, which was stratified into 3 levels.[18] Successful CPB separation was defined as an easy CPB separation, corresponding to the use of only 1 vasoactive or 1 inotropic agent from CPB separation to the end of the surgery. Difficult CPB separation was defined by the use of at least 2 different classes of agents, such as 1 inotrope and 1 vasopressor, from CPB separation to the end of the surgery. Complex CPB separation was defined as a return on CPB or the use of a mechanical circulatory support, such as an intra-aortic balloon pump or a ventricular assist device for hemodynamic purposes. Unsuccessful CPB separation classification corresponds to either a difficult or complex CPB separation. The secondary goal was to determine if pEEG-guided anesthesia leads to a reduction of vasoactive and inotropic administration in the ICU. The vasoactive and inotropic score (VIS) was used to quantify the amount of drugs received by the patient upon their arrival at the ICU. Postoperative complications and outcome definitions are detailed in Supplementary Table 1. Additional outcomes were duration of postoperative intubation, duration of vasoactive support (intraoperative and postoperative), and postoperative organ dysfunction (Supplementary Table 1).

Measures of Vasoactive and Inotropic Pharmacologic Support

During the surgery, doses and concentrations of vasoactive and inotropic drugs were recorded in the electronic patient's chart. These medications were started at the anesthesiologist's discretion based on the patient's clinical history, transesophageal echocardiogram findings, physiological status, hemodynamic parameters, and other characteristics. Upon the patient's arrival in the ICU, the assigned nurse indicated all of the drugs being infused in the patient's chart. Doses and drug concentrations were taken into account for

the first hour in the ICU to allow for the analysis of the secondary outcome of this study. As previously demonstrated,[10,19,20] VIS was calculated as follows: VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 x epinephrine dose (μg/kg/min) + 50 x levosimendan dose (μg/kg/min) + 10 x milrinone dose (μg/kg/min) + 10,000 x vasopressin (U/kg/min) + 100 x norepinephrine dose (μg/kg/min), using the dosing rates of vasoactive and inotropic medications (μg/kg/min or U/kg/min) after ICU admission. The VIS variable was non-normally distributed and was analyzed as a categorical variable to separate patients into the following 3 categories based on scoring intervals, as previously reported: $0 \leq VIS \leq 5$, $5 < VIS \leq 15$, and $VIS > 15$ points.[19]

Processed Electroencephalography (pEEG)

SedLine pEEG monitor (Masimo Corporation) has been introduced at the authors' institution to monitor cerebral electrical activity from the moment they entered the operating room (OR) to their arrival at the ICU. Before the induction of anesthesia, electrodes were placed on the frontal region of the scalp, and anesthetic doses were titrated in order to obtain a patient state index (PSI) value ranging between 25 and 50 and avoid burst suppression. pEEG monitor was not used in the ICU.

Data Management

Demographic and preoperative data were collected from patient medical records. These data included age, cardiovascular risk factors, type of surgery performed, surgery context, European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), and preoperative use of medication, including inotropic and vasoactive drugs. Intraoperative data collected before and after CPB were extracted from the electronic patient record (Compurecord, Philips Healthcare). This included patient hemodynamic data (Supplementary Table 2), brain oximetry and echocardiographic findings prior to and after CPB, fluid balance, cumulative dose of vasopressors, vasodilators, and anesthetic agents used during the surgery, CPB duration, CPB separation classification, and aortic cross-clamp duration. Postoperative data were collected from the patient's medical chart and included the duration of vasopressor requirements, duration of ICU and hospital stay, duration of mechanical ventilation, time of persistent organ dysfunction (TPOD), and VIS.

Statistical Analysis

Descriptive statistics of demographics, hemodynamics, and pharmacologic agents used were presented according to the normality of the distribution of each variable. The quantile-quantile plot was used to test the normality of continuous data. Non-normally distributed data were presented as the median and quartiles (Q1-Q3). Normally distributed data were presented using mean ± standard deviation (SD). Categorical parameters were expressed as frequency (%). For continuous data, groups were compared using a Student's *t* test or the Mann-Whitney *U* test, depending on the data distribution. Pearson's chi-square test was used for categorical variables, and a two-tailed p value < 0.05 was considered statistically significant. Simple analysis of potential risk factors of unsuccessful CPB separation and higher vasoactive and inotropic scores were first produced (results available in Supplementary Table 3). The association between pEEG-guided anesthesia and both outcomes was analyzed using simple and multiple regression models. The dichotomous primary outcome (unsuccessful CPB separation) was analyzed using a logistic regression model. The secondary outcome was analyzed by an ordinal regression model owing to the nature of the VIS variable. Age, left ventricular ejection fraction (LVEF) before the surgery, mean pulmonary artery pressure (MPAP), central venous pressure (CVP), and mean arterial pressure (MAP)-to-MPAP ratio value before CPB, CPB time, and EuroSCORE II were included in both multiple regression models as adjustment terms. CPB time, MAP-to-MPAP ratio, and EuroSCORE II were categorized according to their interquartile range.

The study size calculation was based on local preliminary data, where the incidence of unsuccessful CPB separation was 38% before pEEG implementation. The study authors estimated that the use of pEEG decreases the incidence of unsuccessful separation by 17%. In order to obtain an 80% power with a 5% two-sided significance level, a total of 112 patients were required in each group. The authors decided to include 150 patients in each group. All statistical analyses were performed using SPSS for Mac version 25 (IBM Corp, Armonk, NY) and computer software R (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 300 patients were included in this retrospective study, of which 150 patients were part of the control group, and 150 patients belonged to the pEEG-guided anesthesia group. The preoperative, intraoperative, and postoperative characteristics of the population are summarized in Table 1. There were no differences between the groups in terms of EuroSCORE II, New York Heart Association class III and IV, urgent procedure, and risk factors, such as arterial hypertension, diabetes mellitus, coronary artery disease, and peripheral vascular disease. However, in the pEEG-guided anesthesia group, subjects were older (control: 63 ± 13 *v* pEEG: 67 ± 10, $p = 0.001$), had a higher prevalence of pulmonary arterial hypertension between 31 and 55 mmHg (control: 15% *v* pEEG: 26%, $p = 0.009$), had a higher prevalence of dyslipidemia (control: 61% *v* pEEG: 82%, $p < 0.001$), and concomitant increased statin use (control: 61% *v* pEEG: 75%, $p = 0.006$). On the other hand, patients in the control group had a higher proportion of recent myocardial infarction (control: 24% *v* pEEG: 13%, $p = 0.011$) and more congenital surgery (control: 7% *v* pEEG: 2%, $p = 0.029$) compared to the pEEG-guided anesthesia group. There were no differences in terms of the type of cardiac surgical procedures, such as coronary bypass graft, simple valve, and complex surgery. The median CPB (control: 77 [61-96] minutes *v* pEEG: 80 [58-106] minutes, $p = 0.938$) and aortic cross-clamp duration (control: 55 [38-79] minutes *v* pEEG: 57 [40-83] minutes, $p = 0.618$) were similar be-

Table 1
Demographic and Preoperative Characteristics of the Study Population

	Anesthesia Without pEEG Guidance (n = 150)	Anesthesia With pEEG Guidance (n = 150)	p Value
Age, y	63 ± 13	67 ± 10	0.001
Male sex	114 (76)	117 (78)	0.681
Weight, kg	83 ± 20	83 ± 17	0.841
Height, cm	170 ± 9	168 ± 9	0.185
Body mass index, kg/m^2	29 ± 6	29 ± 6	0.473
Parsonnet	16 ± 12	16 ± 11	0.924
EuroSCORE II	1.9 (1.0-3.5)	1.7 (0.9-3.3)	0.383
New York Heart Association III-IV	8 (5)	7 (5)	0.609
Comorbidities			
• Pulmonary hypertension*	26 (17)	42 (28)	0.016
• Acute kidney injury†	77 (51)	73 (49)	0.644
• Coronary artery disease	103 (69)	113 (75)	0.198
• Atrial fibrillation	24 (16)	25 (17)	0.856
• Diabetes mellitus	44 (29)	47 (31)	0.706
• Arterial hypertension	100 (67)	109 (73)	0.258
• Recent myocardial infarction	36 (24)	19 (13)	0.011
• Left ventricular dilation‡	16 (11)	13 (9)	0.558
• Chronic obstructive pulmonary disease	14 (9)	17 (11)	0.569
• Tobacco smoking	19 (13)	23 (15)	0.491
• Dyslipidemia	91 (61)	123 (82)	<0.001
• Left ventricular ejection fraction above 50%	113 (75)	118 (79)	0.493
• Heart failure with reduced ejection fraction§	37 (25)	32 (21)	0.493
• Peripheral vascular disease	32 (21)	39 (26)	0.342
Medications			
• ACE-I/ARB	81 (59)	81 (59)	1.00
• Statins	91 (61)	113 (75)	0.006
• Aspirin	101 (67)	102 (68)	0.902
• Nitrates	17 (11)	9 (6)	0.101
• Calcium channel blocker	39 (26)	40 (27)	0.896
• Diuretic	41 (27)	38 (25)	0.694
• Antiarrhythmic	9 (6)	6 (4)	0.427
Procedures			
• Urgent surgery‖	27 (18)	24 (16)	0.645
• Coronary artery bypass graft	70 (47)	67 (45)	0.728
• Simple valve	34 (23)	39 (26)	0.501
• Complex surgery¶	35 (23)	41 (27)	0.426
• Congenital surgery	11 (7)	3 (2)	0.029
• Cardiopulmonary bypass duration, min	77 (61-96)	80 (58-106)	0.938
• Cross-clamping time, min	55 (38-79)	57 (40-83)	0.618
• Intraoperative fluid balance, mL	1,233 (702-1,848)	758 (351-1,329)	<0.001
• Baseline brain saturation, %	68 ± 8	69 ± 8	0.629

NOTE. Values are presented as number (percentage). Variables normally distributed are presented as mean ± standard deviation (SD). Variables not normally distributed are presented as median (interquartile range [IQR]).

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Outcomes; pEEG, processed electroencephalography; SD, standard deviation.

* Pulmonary hypertension is defined by systolic pulmonary artery pressure of at least 30 mmHg or a mean pulmonary artery pressure > 25 mmHg, in the preoperative evaluation. In this cohort, 253 patients had a pulmonary artery catheter.

† Acute kidney injury is defined by KDIGO criteria.

‡ Left ventricular dilatations defined as a left ventricular end-diastolic diameter more than 55 mm.

§ Heart failure with reduced ejection fraction is defined as left ventricular ejection fraction inferior to 50%.

‖ Urgent surgery refers to patients not electively admitted for operation but who require surgery on the current admission for medical reasons and cannot be discharged without a definitive procedure.

¶ Complex surgery refers to combination of at least 2 procedures.

tween both groups. Baseline cerebral oximetry saturation was similar between both groups (control: 68 ± 8 *v* pEEG: 69 ± 7.8, p = 0.629).

In the simple analysis, a lower proportion of patients experienced an unsuccessful CPB separation in the pEEG anesthesia-guided group compared to the control group (control: 60% *v* pEEG: 72%, p = 0.028). Within the first hour following ICU admission, patients in the pEEG anesthesia-guided group received less vasoactive and inotropic drugs, resulting in a lower VIS (control: 8 [2 -15] *v* pEEG: 5 [0-10], p = 0.003) (Table 2). Duration of mechanical ventilation (control: 4 [3-7] hours *v* pEEG: 3 [2-4] hours, p < 0.001), intraoperative fluid balance (control: 1,233 [702-1,848] mL *v* pEEG: 758 [351-1,329] mL, p < 0.001) and the amount of bleeding (control: 500 [300-700] mL *v* pEEG: 400 [282-500] mL, p = 0.002) were lower in the pEEG-guided anesthesia group. No difference was found in terms of TPOD (control: 12 [4-35] hours *v* pEEG: 16 [4-42] hours, p = 0.453), mortality (control: 0.7% *v* pEEG: 1.3%, p = 0.562), and duration of vasopressor requirements in the ICU (control: 13 [2-39] hours *v* pEEG: 19 [4-46] hours, p = 0.113).

Table 2
Perioperative Outcomes

	Anesthesia Without pEEG Guidance (n = 150)	Anesthesia With pEEG Guidance (n = 150)	p Value
CPB separation			
• Successful weaning	90 (60)	108 (72)	0.028
• Unsuccessful weaning	60 (40)	42 (28)	0.078
—Difficult—Complex	52 (35)	38 (25)	0.239
	8 (5)	4 (3)	
Intraoperative bleeding, mL	500 (300-700)	400 (282.5-500)	0.002
Postoperative outcomes			
• Vasoactive Inotropic Score (VIS) at ICU admission*	8 (2-15)	5 (0-10)	0.003
• Duration of mechanical ventilation, h	4 (3-7)	3 (2-4)	<0.001
• Delirium	17 (11)	23 (15)	0.297
• TPOD†	12 (4-35)	16 (4-42)	0.453
• Vasopressor time, h	13 (2-39)	19 (4-46)	0.113
• Length of stay in the ICU, d	2 (1-4)	2 (1-4)	0.877
• Length of hospital stay, d	6 (5-8)	6 (5-8)	0.517
• Death	1 (0.7)	2 (1.3)	0.562

NOTE. Values are presented as number (percentage). Variables normally distributed are presented as mean (standard deviation [SD]). Variables not normally distributed are presented as median (interquartile range [IQR]).

Abbreviations: CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; pEEG, processed electroencephalography; POD, persistent organ dysfunction; SD, standard deviation; TPOD, death during the first 28 days; VIS, vasoactive inotropic score.

* Vasoactive Inotropic Score is defined as VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 x epinephrine dose (μg/kg/min) + 50 x levosimendan dose (μg/kg/min) + 10 x milrinone dose (μg/kg/min) + 10,000 x vasopressin (μg/kg/min) + 100 x norepinephrine dose (μg/kg/min).

† Time with persistent organ dysfunction (POD) or death during the first 28 days (TPOD) is defined by Stoppe et al[21] as 1 or more of the following: mechanical ventilation; vasopressor therapy (ongoing need for vasopressor agents such as norepinephrine, epinephrine, vasopressin, dopamine >5 μg/kg/min, or phenylephrine > 50 μg/min); mechanical circulatory support (ongoing need for mechanical devices such as extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pump; new continuous renal replacement therapy or new intermittent hemodialysis (first to last dialysis session). Therefore, TPOD represents the time for which the patient requires invasive life support after cardiac surgery. TPOD is a continuous variable representative of the burden of care and morbidity during the first 28 days following cardiac surgery and was chosen to circumvent issues arising from using other clinical endpoints, such as intensive care unit (ICU) length of stay.

In the control group, patients with RV dysfunction or pulmonary hypertension received less inhaled epoprostenol before CPB (control: 44% *v* pEEG: 81%, p < 0.001). However, they required more inhaled epoprostenol after CPB (control: 17% *v* pEEG: 7%, p = 0.013) (Supplementary Table 4). The control group received less inhaled milrinone prior to CPB (control: 45% *v* pEEG: 63%, p = 0.002), but there were no differences after CPB. Patients in the control group received more propofol (control: 27 [21-34] μg/kg/min *v* pEEG: 25 [19-30] μg/kg/min, p = 0.001) during the procedure compared to patients in the pEEG-guided anesthesia group. During surgery, patients in the control group received more fentanyl (control: 0.07 ± 0.05 μg/kg/min *v* pEEG: 0.05 ± 0.02 μg/kg/min, p < 0.001), and norepinephrine (control: 0.06 [0.04-0.09] μg/kg/min *v* pEEG: 0.05 [0.02-0.08] μg/kg/min, p = 0.039). However, they also received less vasopressin (control: 0.95 ± 0.67 U/h *v* pEEG: 1.37 ± 0.90 U/h, p < 0.001) and smaller doses of nitroglycerin (control: 0 [0-0.02] μg/kg/min *v* pEEG: 0.06 [0.006-0.16] μg/kg/min, p < 0.001).

In the multiple logistic regression, use of pEEG-guided anesthesia was not independently associated with successful CPB separation (odds ratio [OR] = 0.59; 95% confidence interval [CI]: 0.3-1.16; p = 0.12) (Table 3). From that analysis, the odds of having an unsuccessful CPB separation was greater among people with a preoperative LVEF lower than 50%, higher MPAP before CPB (OR = 1.08; 95% CI: 1.0-1.16; p = 0.04), and longer CPB duration (OR = 3.26; 95% CI: 1.20-8.82; p = 0.02).

In the multiple ordinal regression analysis, pEEG-guided anesthesia was associated with lower use of vasoactive and inotropic drugs at the ICU arrival (Table 3). A pEEG-guided anesthesia reduced the odds of being in a higher VIS category by 57% (OR = 0.43; 95% CI: 0.26-0.73; p = 0.002). Also, the odds of being in a higher VIS category was greater among people with a LVEF lower than 50% (OR = 2.03; 95% CI: 1.08-3.85; p = 0.03) and with a longer CPB duration (OR = 3.81; 95% CI: 1.83-8.11; p < 0.001).

Discussion

The main finding of this study is that pEEG-guided anesthesia was not associated with more successful CPB separation when adjusted for other parameters. Instead, abnormal LVEF, high MPAP values before CPB, and longer CPB duration were associated with unsuccessful CPB separation. Those parameters had already been reported as independent predictors of hemodynamic complications and difficult separation from CPB during cardiac surgery.[22-25] Successful CPB separation is defined by the use of 1 or fewer pharmacologic agents during CPB separation. It is possible that the amount of agents the patient received upon arrival to the ICU is a better predictor of poor prognosis than the administration of a single bolus during CPB separation. Indeed, patients with a higher VIS had a longer TPOD compared to patients in a lower VIS category (Supplementary Tables 5 and 6). However, other factors, such as myocardial protection and air embolism from suboptimal de-airing maneuvers, may influence the ease of separation from CPB independently of pEEG.[26]

However, pEEG-guided anesthesia in cardiac surgery is associated with a reduction in the odds of having a higher amount of vasoactive and inotropic drug requirement at ICU arrival. A randomized controlled trial of 66 patients undergoing cardiac surgery using CPB demonstrated that a need for inotropic support after CPB was higher in patients with a BIS between 35 and 44 compared with pa-

Table 3
Multiple Analysis of Risk Factors of Unsuccessful CPB Separation and Higher Vasoactive and Inotropic Score

Multivariable Analysis of Unsuccessful CPB Separation			
Risk factors	OR	95% CI	p Value
Anesthesia with pEEG guidance	0.59	0.3-1.16	0.124
Age, y	1.01	0.97-1.05	0.693
Left ventricular ejection fraction inferior to 50%	2.32	1.02-5.27	0.044
Mean pulmonary arterial pressure before CPB >30 mmHg	1.08	1-1.16	0.039
Central venous pressure before CPB, mmHg	1.02	0.94-1.11	0.585
Cardiopulmonary bypass duration, reference: 23-60 min*			
• CPB duration between 61-78 min	2.36	0.89-6.28	0.085
• CPB duration between 79-102 min	2.29	0.9-5.83	0.083
• CPB duration between 103-550 min	3.26	1.2-8.82	0.02
Mean arterial pressure/Mean pulmonary arterial pressure reference: 3.7-10.9*			
• MAP-to-MPAP ratio between 1-2.6	2.05	0.49-8.55	0.325
• MAP-to-MPAP ratio between 2.7-3.2	0.55	0.17-1.81	0.329
• MAP-to-MPAP ratio between 3.3-3.7	0.86	0.3-2.45	0.783
EuroSCORE II reference: 0.5-0.985*			
• EuroSCORE II between 0.986-1.79	1.62	0.61-4.31	0.333
• EuroSCORE II between 1.80-3.5	0.86	0.29-2.57	0.791
• EuroSCORE II between 3.6-53.8	2.48	0.78-7.89	0.125
Multivariable analysis of higher vasoactive and inotropic score †			
Risk factors	OR	95% CI	p Value
• Anesthesia with pEEG guidance	0.43	0.26-0.73	0.002
• Age, y	1.01	0.98-1.04	0.377
• Left ventricular ejection fraction inferior to 50%	2.03	1.08-3.85	0.028
• Mean pulmonary arterial pressure before CPB >30 mmHg	1.01	0.96-1.06	0.717
• Central venous pressure before CPB, mmHg	0.98	0.92-1.04	0.455
Cardiopulmonary bypass duration, reference: 23-60 min*			
• CPB duration between 61-78 min	1.73	0.86-3.53	0.127
• CPB duration between 79-102 min	1.19	0.59-2.38	0.620
• CPB duration between 103-550 min	3.81	1.83-8.11	<0.001
Mean arterial pressure and/or mean pulmonary arterial pressure reference: 3.7-10.9*			
• MAP-to-MPAP ratio between 1-2.6	1.93	0.62-6.09	0.258
• MAP-to-MPAP ratio between 2.7-3.2	0.73	0.30-1.77	0.490
• MAP-to-MPAP ratio between 3.3-3.7	1.86	0.87-4.04	0.113
EuroSCORE II reference: 0.5-0.985*			
• EuroSCORE II between 0.986-1.79	1.04	0.50-2.18	0.912
• EuroSCORE II between 1.80-3.5	1.16	0.54-2.51	0.698
• EuroSCORE II between 3.6-53.8	1.93	0.80-4.69	0.143

Abbreviations: CI, confidence interval; CPB, cardiopulmonary bypass; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; OR, odds ratio; pEEG, processed electroencephalography; VIS, vasoactive inotropic score.

* The variable has been categorized according to interquartile range.

† The vasoactive and inotropic score (VIS) has been categorized in 3 categories, which the first category represents VIS between (0-5), the second category a VIS between (6-15), and the third category a VIS above 15. A higher VIS corresponds to a patient with a VIS value in the second and third category compared to the first category or a patient with a VIS value in the third category compared to the first and second category.

tients with a BIS between 45 and 55.[27] This finding indicates that patients with lower BIS values, corresponding to patients receiving more anesthetic agents, had higher dobutamine requirements after the surgery. It is well known that propofol, which was more used in the control group, reduces myocardial contractility and reduces blood pressure by inhibiting catecholamines, which are synthesized by the sympathetic nerve terminals and by adrenal medullary cell.[28] The lower level of endogenous catecholamines decreases systemic vascular resistance and cardiac contractility and, therefore, may explain the higher dose of inotrope agents administered to patients who did not have pEEG-guided anesthesia.

PSI and BIS are both used to quantify the depth of anesthesia and are used to tailor the amount of anesthetic drugs given during surgery. Both monitors have the same predictive value regarding the level of sedation; they apply different algorithms.[29] To ensure consistency in the cohort selection, all patients in the treatment group were monitored with the same pEEG device (SedLine; Masimo) that uses the PSI to assess the depth of anesthesia.

To the authors' knowledge, no previous studies primarily explored the effect of pEEG-guided anesthesia on vasoactive and inotropic drug usage in the ICU. The hypothesis that led to this study is that if the use of pEEG-guided anesthesia is able to reduce inotropic use during cardiac surgery, these patients might also receive less vasoactive and inotropic agents at their arrival in the ICU and, hence, have better postoperative outcomes. The reduction in the duration of ventilation in the pEEG group could also be associated with a lower VIS score, as hemodynamically stable patients can be extubated earlier. In the regression model, lower LVEF before the surgery and longer CPB duration were also associated with increased odds of being in a higher VIS category. It is well documented that reduced LVEF is an independent predictor for prolonged vasopressor support in cardiac surgery.[30] All patients under CPB will experience systemic inflammatory response that can be exacerbated by CPB duration, which is an important parameter correlated with hemodynamics complications and poor outcomes.[31,32] This explains why patients with longer CPB are more likely to be in a high VIS

category. In a retrospective cohort study of 129 adult cardiac surgery patients, a high-VIS at the end of surgery was associated with poor outcomes and a longer ICU stay.[33] The authors know that mortality rates and renal dysfunction are increased when high doses of vasoactive drugs are required in the postoperative period. For these reasons, pEEG-guided anesthesia may be associated with reduced postoperative complications. However, in this study, the authors did not observe any difference in postoperative organ dysfunction between the 2 groups.

It is well documented that pEEG-guided anesthesia during cardiac surgery reduces the use of anesthetic agents, such as propofol,[3,4] sevoflurane,[11] desflurane, and isoflurane.[34] The present study observed the same findings. In the authors' study, they also observed that patients with pEEG-guided anesthesia received less intraoperative fluid compared to patients without pEEG. This, in conjunction with the higher use of inhaled epoprostenol and milrinone, could explain lower CVP and MPAP after CPB. This difference between the 2 groups may be owing to changes in practice over time. Nevertheless, by giving fewer anesthetic agents, patients may experience fewer hypotensive episodes, and clinicians may thus reduce intravenous fluid administration during the surgery.

Also, in this study, the duration of mechanical ventilation in the ICU was shorter for patients with intraoperative pEEG monitoring. This association would require confirmation. Other factors may contribute to the shorter duration of mechanical ventilation. Patients in the pEEG-guided anesthesia group experienced less intraoperative bleeding compared to patients in the control group. This observation may be secondary to the change in anesthesiologist practice following pEEG introduction in the OR. As mentioned previously, pEEG-guided anesthesia reduces the amount of anesthetic agents, and, therefore, fewer vasopressor agents and intraoperative volumes are given to the patient during cardiac surgery. Thereby, in the pEEG-guided anesthesia group, CVP is lower after CPB compared to patients in the control group. During cardiac surgery, blood loss is mostly from the venous compartment, as suggested by studies showing a relationship between venous pressure and bleeding.[35-37] By giving fewer intraoperative fluids and more inhaled pulmonary vasodilator agents in the OR, the ensuing lower CVP may be associated with blood loss reduction.[35,38] Also, a decrease in CVP may be caused by a higher administration of nitroglycerin in the pEEG-guided anesthesia group.

This study has several limitations. It was a retrospective single-institution study with clinicians unfamiliar with the use of pEEG before 2017. Several biases and uncontrolled confounding factors can be present in retrospective studies; however, if the result is positive, it has to be seen as an initial step before performing a clinical trial that is underway. Moreover, data were based on pEEG and not on raw EEG, which is more accurate in determining the depth of anesthesia. Also, pEEG does not necessarily reflect the analgesic requirements of a patient. There is some evidence that pain increases pEEG activity, but there was no nociception monitor used in this study.[39] Most recent studies have shown that the BIS index monitor was less effective in detecting standardized noxious stimuli than nociception monitor, such as the nociception level index.[40] The authors decided to use the VIS to quantify the amount of vasoactive and inotropic agents received upon patient arrival in the ICU. Even if the VIS is a good predictive value for mortality in critically ill patients, there are other methods for defining the degree of cardiovascular support.[10,21,41] In this study, one of the strengths of VIS is that the management of vasoactive and inotropic drugs is done by the intensive care staff and not by the anesthesiologist in the OR. The authors did not extract the end-tidal volatile agent concentration and calculate the minimal alveolar concentration for each patient because it was not available during CPB, and the authors' anesthesia technique is based on a combination of both volatile and intravenous agents for which they do not measure plasmatic concentration. The intensive care team did not know if the anesthesia was pEEG guided in the OR and did not use the monitor on their unit. Also, even if the 2 groups are comparable, they have not been matched. The authors had been using a 30 mmHg threshold for abnormal MPAP before the new guidelines suggested a 20 mmHg value.[42] Finally, the PSI and the burst-suppression time values were not recorded and analyzed but interpreted in real-time by the attending anesthesiologist. Therefore, it is difficult to conclude the effectiveness of pEEG guided anesthesia. The study authors want to explore the impact of a pragmatic value of introducing this monitor in the cardiac OR.

Conclusion

In this study, pEEG-guided anesthesia is associated with a reduction in the use of inotropic or vasoactive drugs at arrival in the ICU. In addition, its implementation was associated with a lower requirement of anesthetic agents and opioids in the OR, lower CVP, fluid requirements, intraoperative bleeding, and a shorter duration of mechanical ventilation. However, its use did not facilitate weaning from CPB compared to a group where pEEG was unavailable. Future research is needed to confirm these results in prospective randomized clinical trials.

Conflict of Interest

Dr. Denault is a speaker and consultant for CAE Healthcare, speaker for Edwards and Masimo. He received a research grant from Edwards (2019).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.jvca.2022.03.030.

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