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ORIGINAL RESEARCH

Intraoperative reduction of vasopressors using processed electroencephalographic monitoring in patients undergoing elective cardiac surgery: a randomized clinical trial

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Abstract

Intraoperative vasopressor and fluid application are common strategies against hypotension. Use of processed electroencephalographic monitoring (pEEG) may reduce vasopressor application, a known risk factor for organ dysfunction, in elective cardiac surgery patients. Randomized single-centre clinical trial at Jena University Hospital. Adult patients operated on cardiopulmonary bypass or off-pump coronary artery bypass grafting were randomised to receive anesthesia with visible or blinded pEEG using Narcotrend™. In blinded-Narcotrend (NT) depth of anesthesia was extrapolated from clinical signs, hemodynamic response and anesthetic concentration, supplemented by target indices between 37 and 64 in the visible-NT group. Intraoperative norepinephrine requirement (primary endpoint), fluid balance, extubation time, delirium occurrence and adverse events were evaluated. Patients of the intent-to-treat population (visible-NT: n = 123, blinded-NT: n = 122) had similar patient and procedural characteristics. Adjusted for type of surgery intraoperative Norepinephrine application was significantly reduced in visible-NT (n = 120, robust mean of cumulative dose 4.71 µg/kg bodyweight) compared to blinded-NT patients (n = 119, 6.14 µg/kg bodyweight) (adjusted robust mean difference 1.71 (95% CI 0.33–3.10) µg/kg bodyweight). Although reduction in patients operated on cardiopulmonary bypass was higher the interaction was not significant in post-hoc subgroup analysis. Intraoperative fluid balance was similar among both groups and strata. Extubation time was non-significantly lower in visible than in blinded-NT group. Overall postoperative delirium risk was 16.4% without differences among the groups. Adverse events—sudden movement/coughing, perspiration or hypertension—occurred more often with visible-NT, while one blinded-NT patient experienced intraoperative awareness. Titration of depth of anesthesia in elective cardiac surgery patients using pEEG allows to reduce application of norepinephrine.

Keywords Cardiac anesthesia · Neuromonitoring · Catecholamines · Adverse events

1 Introduction

Anesthetic drug administration aims to reduce patients' physiologic response to surgical stimuli and modern anesthesia has allowed to conduct even complex procedures in an increasingly older patient population with significant comorbidities. One major adverse event associated with anesthetics is hypotension [1], increasing the severity of cardiovascular complications in non-cardiac surgery [2]. Regarding cardiac surgical patients hypotension and vasopressor dependency > 3 h after cardiac surgery enhanced postoperative complications (i.e. renal dysfunction) and prolonged ICU stay [3]. Moreover, administration of vasopressors to counteract vasoplegic shock provided the risk of

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developing organ dysfunction [4] and led to arrhythmias and myocardial ischemia [5].

Optimal depth of general anesthesia is defined carrying a low risk of intraoperative recall and maintenance of blood pressure and heart rate at acceptable levels with minimal intervention [6]. This definition includes lack of movement to surgical stimuli, although our ability to assess this is impaired with the use of neuromuscular blockers. Depth of anesthesia is mainly extrapolated from clinical signs, hemodynamic response and concentration of inhaled or intravenous anesthetics [7], often supplemented by the use of processed electroencephalographic monitors (pEEG). PEEG was designed to reduce intraoperative awareness following anesthetic underdosage [8] and provide additional information in the form of index values and burst suppression on the raw EEG [9]. Up to date, several pEEG monitors are available, using different algorithms and features to measure depth of anesthesia [10]. The algorithm of the Narcotrend (NT) Monitor is based on pattern recognition of the raw EEG, which is further classified into stages ranging from A (awake) to F. Additionally, an Index value between 0 and 100 is provided. Reference values of the Index for general anesthesia range between 37 (stage D2) and 64 (stage D0) [11]. Moreover, the Narcotrend monitor also dispalys information on the electromyogram (EMG) [10].

Although vasopressor support is associated with adverse events [3, 12], the cause-effect relationship remains elusive. It seems more likely that the need to use vasopressors indicates depression of the cardiovascular system due to inappropriate depth of anesthesia which in turn promotes organ dysfunction. In any case, pEEG may be useful to prevent untoward effects of anesthesia by reducing vasopressor support through individualized anesthetic dosage. Previous studies already reported on less vasopressor requirement when using pEEG guided anesthesia, however, not as a primary study endpoint [13, 14].

This randomised clinical trial aimed to investigate intraoperative use of NT on vasopressor requirement in patients undergoing elective cardiac surgery. We hypothesised a 30% vasopressor reduction to maintain mean arterial blood pressure (MAP) between 65 and 85 mmHg during surgery using NT guided anesthesia with predefined index values. As secondary endpoints we investigated fluid balance, time to tracheal extubation, occurrence of postoperative delirium and adverse events (i.e. intraoperative awareness).

2 Materials and methods

2.1 Study design and eligibility criteria

The study was designed as a single-centre, 1:1 randomised, open-label, interventional trial. It was approved by the local ethics committee (No. 4468-06/15) and registered at the German Clinical Trial Register (http://www.drks.de) with the identifier code DRKS00009232 on 19-August-2015.

The study was investigator initiated, with external support of Narcotrend (Hannover, Germany), which provided the NT modules for intraoperative usage. NarcotrendTM had no role in data collection, analysis and quality control.

Inclusion criteria were: elective cardiac surgery with an expected cardiopulmonary bypass (CPB) time ≤ 180 min or elective off-pump coronary artery bypass grafting (OPCAB), age ≥ 18 years and written informed consent. Exclusion criteria included: Planned cardiac surgery using hypothermic circulatory support or cardiac arrest, expected CPB time > 180 min, non-elective surgery, concurrent interventional trials and refusal to participate.

2.2 Patient recruitment and randomization

The statistician generated the allocation sequence by a computer algorithm (nQuery Advisor 7.0). Allocation was stratified by the two types of surgery (surgery with CPB (i.e. valve surgery, on pump bypass grafting) and OPCAB) and blocked by randomly selected block sizes. All patients scheduled for elective cardiac surgery were asked to participate in the study when presenting during the preoperative assessment. After reviewing the in- and exclusion criteria, all participants signed informed consent. On the day of surgery patients were randomly allocated to the treatment arm or conventional anesthesiologic care before onset of anesthesia. An independent person managed the allocation procedure to keep the list concealed.

2.3 Anesthesiologic management

All anesthesiologists were comfortable in managing anesthesia for cardiac surgery without the use of pEEG and adherence to the local standard operating procedure (SOP) as depicted in Table 1. Narcotrend was implemented prior study initiation and all anesthesiologists were trained in benefits and limits of the method.

Patients admitted to the operating theatre received oral medication of midazolam (3.75–7.5 mg) except those with an age > 75 years, obstructive sleep apnoea disorder or severely impaired cardio-pulmonary reserve. After implementing standard cardiopulmonary monitoring (including 5-lead electrocardiogram and peripheral oxygen saturation) and pEEG electrodes all patients were placed on an intravenous crystalloid infusion. Depending on the patient´s condition, scheduled operation and surgical approach either the radial, femoral or axillary artery were cannulated for invasive blood pressure measurement. After preoxygenation, anesthesia was induced with sufentanil, propofol and pancuronium or rocuronium according to the

Table 1 Standard operating procedure for anesthesiologic drug management in both randomization groups

	Blinded-NT according to local SOP	Visible-NT lowest acceptable dose
Sufentanil—induction dose [µg/kg BW]	1	0.5
Sufentanil—continuous application [µg/kg BW/h]	0.7–1	0.5
Propofol—induction dose [mg/kg BW]	2	0.5
Propofol—continuous application during CPB [mg/kg BW/h]	5	2.5
Sevoflurane—inhalation [MAC]	0.5–1	0.4
Norepinephrine or volume challenge to achieve MAP of	65 mmHg	65 mmHg

BW bodyweight, *CPB* cardiopulmonary bypass, *MAC* minimal alveolar concentration, *MAP* mean arterial blood pressure

SOP (see Table 1). In case of CPB surgery anesthesia was maintained using inhaled sevoflurane and i.v. sufentanil prior to CPB. With onset of CPB patients were placed on propofol and sufentanil infusion, while sevoflurane inhalation was terminated. In OPCAB surgery, anesthesia was maintained using inhaled sevoflurane and sufentanil infusion throughout the procedure. None of the patients received further neuromuscular blockade except the initial dose. According to our clinical SOP and based on results from a survey evaluating catecholamine and fluid therapy during CPB [15], a MAP between 65 and 85 mmHg was aimed throughout the anesthesiologic management using either a volume challenge (assessed by using echocardiography, central venous pressure and urine output) or vasopressor infusion (Norepinephrine) or inotropic (ephedrine, milrinone, epinephrine) support. After surgery all patients were transferred to the intensive care unit (ICU) under sedative medication (propofol infusion) and controlled ventilation.

2.4 Surgical procedure and CPB

All patients underwent surgery according to the SOP of the department of cardio-thoracic surgery. Access to the heart was established either via classic midline sternotomy, or right- or left-sided thoracotomy, depending on the type of operation. OPCAB patients received a loading dose of 300 IU/kg unfractionated heparin plus additional doses to reach and maintain a target activated clotting time (ACT) $\geq$ 300 s. In on-pump cases, CPB was established after a loading dose of 400 IU/kg of unfractionated heparin plus additional doses to reach and maintain a target ACT $\geq$ 400 s. CPB priming volume was composed of 1100 ml Ringers lactate, 200 ml Mannitol, 1000 IU Heparin, 20 ml sodiumbicarbonate and 1000 mg tranexamic acid. After CPB weaning or finishing the anastomoses (in OPCAB) protamine was administered in a 1:1 ratio. Additionally, all patients received 1000 mg of tranexamic acid before chest closure.

2.5 Interventions

According to the random allocation, pEEG was either visible for the anesthesiologist (visible-NT) or blinded and recorded (blinded-NT). In case of visible-NT application of intraoperative anesthesiologic medication was aimed to be dosed resulting in Narcotrend indices (NI) between 37 and 64—as prescribed for general anesthesia. In case of higher NI (> 64) anesthetic medications were increased and they were reduced in case of NI < 37 as far as predefined lower dose limits (see Table 1) or the aforementioned range of the NI was reached. Patients allocated to blinded-NI received standard anesthesiologic management and medication according to a SOP (see Table 1). In case of non-responding hypotension or heart failure, the anesthesiologist was able to apply other vasoactive drugs (i.e. vasopressin or ephedrine) or inotropes (i.e. epinephrine, milrinione) as appropriate. NI, doses of sufentanil, propofol and catecholamines, as well as exhaled concentration of sevoflurane were recorded at defined time points (see S1 table). After surgery doses of applicated medications, fluids and transfusions were recorded. The anesthesiologist was able to record intraoperative incidents in a free text format. All of these incidents were summarized and post hoc evaluated as intraoperative adverse events. Moreover, time on CPB, aortic cross-clamping time and fluid balance on CPB were recorded. After ICU referral all patients underwent standard medical care. Noteworthy, cardiac surgeons, CPB technicians and ICU-personnel were blinded regarding treatment. Fluid application, transfusion requirement, urine output, time to extubation and CAM-ICU [16] were recorded. Within 3 days after tracheal extubation all patients underwent a personal survey using the Brice questionnaire regarding possible awareness [17]. Patient charts were screened for the appearance of postoperative delirium and survival.

2.6 Study endpoints

The primary endpoint was intraoperative norepinephrine requirement following anesthetic drug administration

resulting in NI between 37 and 64. Secondary endpoints comprised intraoperative fluid balance, time to extubation, the appearance of postoperative delirium and intraoperative adverse events [defined as intraoperative events differing from normal anesthesia (i.e. sudden movement, coughing)].

2.7 Sample size and statistical analysis

We used pilot data from 23 patients undergoing elective cardiac surgery without pEEG (n = 13 on-pump valve surgery, n = 10 off-pump bypass surgery, mean cumulative intraoperative Norepinephrine requirement 8.45 (standard deviation 6.6) µg/kg bodyweight) to calculate the sample size. To detect a clinical relevant reduction of 30% (2.54 µg/kg bodyweight) with 80% power 107 patients were needed in each group using a two group t-test with a 0.05 two-sided significance level. To compensate for dropout and lower efficiency of Mann–Whitney U test 126 patients should be allocated per group.

Baseline data of patients and characteristics of surgery were described by statistical measures according to scale. Due to the skewed distributions with zero data and differences in location and scale the primary endpoint was finally analysed by robust regression using Huber-M-estimation and including type of surgery as covariate [18]. The adjusted robust location difference with 95% confidence interval was estimated as effect measure by the regression coefficient for intervention. Post-hoc, subgroup analysis for type of surgery was done by adding an interaction term to the regression model. Secondary endpoints were compared by Mann–Whitney U test, logrank test for right censored time to extubation data or Chi2 test. We quantified effects of intervention by (i) the median of all possible differences of group- specific individual data, which can be interpreted as the difference of medians in case of distributions that are identical in shape but differ in location [19] or (ii) the relative risk with 95% confidence intervals, respectively. Endpoint data were further displayed in subgroups of OPCAB and CPB without statistical testing. An intent-to-treat analysis was planned but modified by excluding patients for reasons which became obvious after randomization. Due to small but different numbers of missing data for several endpoints we used complete cases with valid endpoint data for the final analyses, respectively.

Two-tailed p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS English version 9.4 (SAS Institute Inc., Cary, NC, USA) and SigmaPlot version 13.0 (Systat Software, Erkrath, Germany).

3 Results

3.1 Patients and randomization

Figure 1 summarizes the patient progress through the trial. Patient enrollment started on 06- October-2015 and was finished on 03-June-2016. Seven patients were excluded after randomization: One patient spent > 3 h on CPB, three OPCAB patients had complex and very long surgery (resulting in severe systemic inflammatory response syndrome), two patients underwent intraoperative cardiopulmonary resuscitation, one patient was included in another clinical trial. The final analysis included n = 245 patients, n = 123 in the blinded-NT group and n = 122 in the intervention group with visible-NT. Two patients, one in each group, allocated for OPCAB underwent surgery with CPB. Characteristics of patients and surgery summarized in Table 2 were balanced in the two groups.

3.2 Primary endpoint—catecholamine support

Patients allocated to blinded-NT showed a robust mean intraoperative Norepinephrine requirement of 6.14 µg/kg (0.037 µg/kg/min) to maintain MAP between 65 and 85 mmHg (n = 119 patients). Patients allocated to visible-NT received a robust mean Norepinephrine dose of 4.71 µg/kg (0.025 µg/kg/min) (n = 120 patients). Robust regression revealed a significant location difference (blinded-visible), adjusted for type of surgery, of 1.71 (95%CI 0.33 to 3.10) µg/kg (p = 0.015). Using pEEG norepinephrine application was relatively reduced by about 28% in the visible compared to the blinded-NT group (robust location difference of 1.71 divided by the robust location estimation of the blinded-NT group of 6.14). On CPB intraoperative norepinephrine application was reduced by 2.44 (95%CI 0.74 to 4.14) µg/kg in the visible-NT compared to the blinded-NT group. In patients undergoing OPCAB surgery reduction was 0.82 (95%CI − 1.37 to 3.01) µg/kg. There was no evidence of statistically different effects (p-interaction = 0.20). Figure 2 and Table 3 summarize the norepinephrine requirement of both randomization groups and strata. The incidence of heart failure requiring inotrope medication was n = 6 patients (n = 2 in blinded-NT and n = 4 in the visible-NT group, p = 0.403).

Accompanied with the reduction of Norepinephrine the vasodilative agents (urapidil and nitroglycerine) were significantly more frequently applicated due to hypertension (MAP ≥ 85 mmHg) in visible NT-group (n = 38) compared to the blinded-NT group (n = 20), most likely during the cannulation process for CPB. The use of other vasoactive agents was similar among the groups (see Table 4).

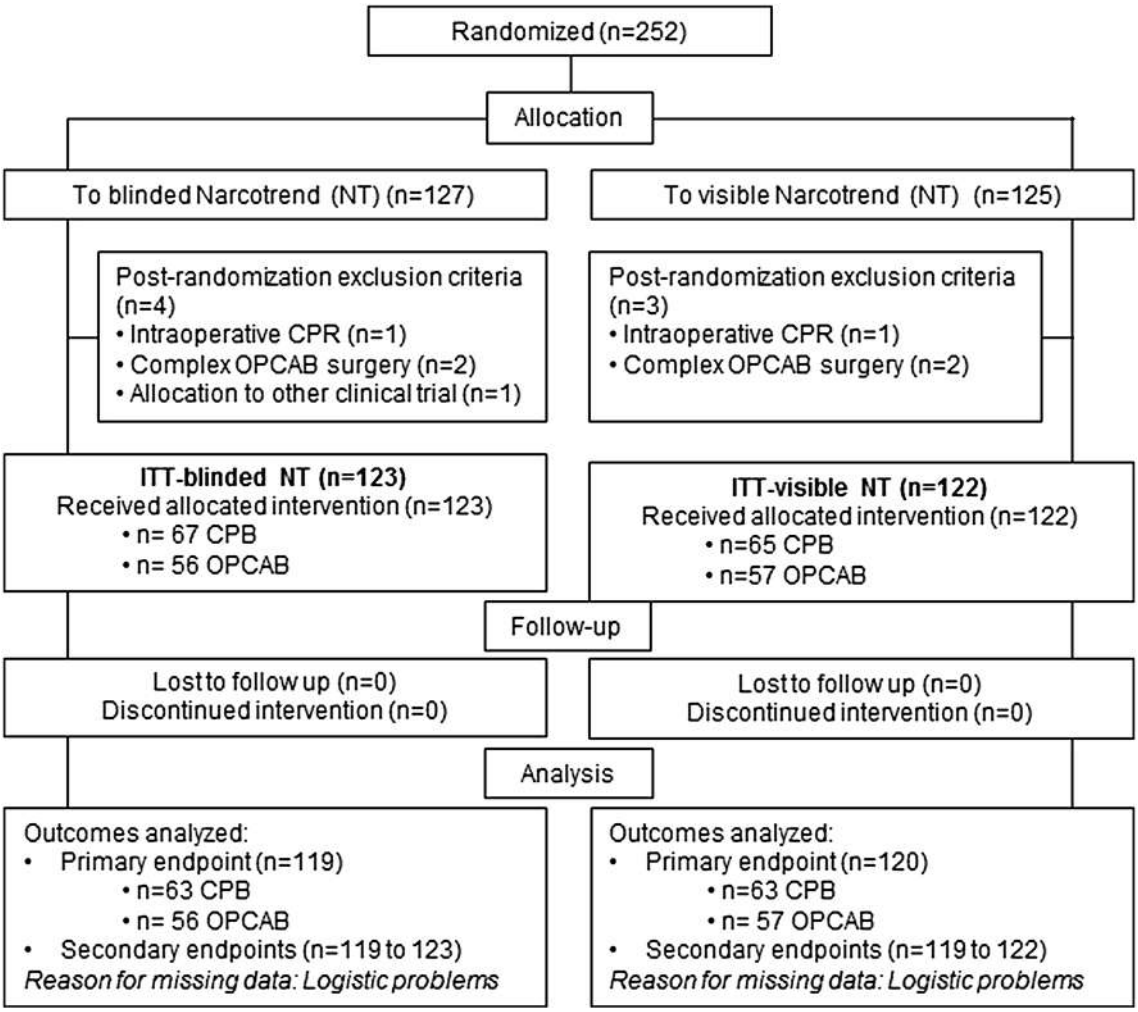

Fig. 1 Patient progress through the trial (*OPCAB* off-pump coronary artery bypass grafting, *CPB* cardiopulmonary bypass, *ITT* intent-to-treat)

3.3 Secondary endpoints

Patients allocated to blinded-NT received a median amount of 5801 ml crystalloid fluid within the perioperative period (including surgery, CPB balance and the first 12 h ICU treatment). Patients in the visible-NT group received 5442 ml of crystalloid fluid within the same period (Table 3). The reduction of 109 (95% CI − 462 to 671) ml was statistically not significant. Moreover, we found no differences regarding transfusion of red blood cells or plasma products (see S2 Table).

The median time on postoperative mechanical ventilation was slightly reduced from 305 min in the control group to 275 min in the visible-NT group resulting in a reduction of 40 (95% CI 0 to 75) minutes ($p = 0.062$).

The incidence of postoperative delirium—defined by a positive CAM-ICU—was 16.4%. Twenty patients of the blinded-NT group and 19 patients allocated to the visible-NT group developed postoperative delirium ($p = 0.75$). Out of 39 patients with delirium 17 (43.6%) suffered from hyperdynamic, 15 (38.5%) from hypodynamic and 7 (17.9%) from mixed delirium. No differences were observed between treatment arms. The majority of patients underwent uneventful anesthesia and surgery. However, in $n = 13$ patients the anesthesiologist reported on adverse events: Three patients in the visible-NT group presented unexpected NI increase (> 70) accompanied by hypertension (MAP ≥ 85 mmHg) despite a hitherto normal anesthesia. Eight patients (thereof seven in the visible-NT group) showed unexpected movement/coughing/breathing and two patients (one of each group) presented perspiration despite low NI. Adverse events were more common in the visible-NT group (11/122) compared to the blinded-NT group (2/123) ($p = 0.010$). Using Brice questionnaire none of the patients allocated to the visible-NT group reported awareness. One patient of the blinded-NT group reported signs hinting to awareness during anesthesia. Evaluating the referring cerebrogram hinted

Table 2 Patient characteristics and description of surgery according to intervention

	Blinded-NT n = 123	Visible-NT n = 122
Patient		
Age (years), median (25th–75th percentile)	68 (62–75)	68 (59–75)
Male gender, n (%)	86 (69.9)	88 (72.1)
BMI (kg/m^2), median (25th–75th percentile)	27.8 (24.6–30.8)	27.7 (25.1–30.1)
Euroscore, median (25th–75th percentile)	6 (3–8)	5 (3–7)
COPD, n (%)	23 (18.7)	18 (14.8)
Extracardiac arteriopathy, n (%)	38 (30.9)	32 (26.2)
Neurologic dysfunction, n (%)	10 (8.1)	12 (9.8)
Previous cardiac surgery, n (%)	6 (4.9)	5 (4.1)
Unstable angina pectoris, n (%)	17 (13.8)	16 (13.1)
LVEF, n (%)		
> 50	83 (67.5)	83 (68.0)
30–50	36 (29.3)	33 (27.0)
< 30	4 (3.3)	6 (4.9)
Myocardial infarction, n (%)	21 (17.1)	18 (14.8)
Pulmonary hypertension, n (%)	28 (22.8)	22 (18.0)
Additional intervention, n (%)	15 (12.2)	20 (16.4)
Initial heart rhythm, n (%)		
Sinus	100 (81.3)	105 (86.1)
Atrial fibrillation	18 (14.6)	13 (10.7)
Pacemaker	4 (3.3)	2 (1.6)
Other	1 (0.8)	2 (1.6)
Surgery		
OPCAB, n (%)	56 (45.5)	57 (46.7)
CPB, n (%)	67 (54.5)	65 (53.3)
Subtype of surgery on CPB, n (%)		
Single valve	33 (26.8)	33 (27.1)
Single valve + CABG	11 (8.9)	12 (9.8)
CABG	7 (5.7)	6 (4.9)
Double valve	7 (5.7)	8 (6.6)
Single valve + ascending aortic repair	5 (4.1)	2 (1.6)
Double valve + CABG	2 (1.7)	3 (2.5)
Ascending aortic repair	1 (0.8)	0 (0.0)
Triple valve	1 (0.8)	1 (0.8)
Duration of CPB (min), median (25th–75th percentile)	107 (94–128)	117 (94–144)
Cross clamping time (min), median (25th–75th percentile)	64 (50–78)	66 (52–81)
Duration of surgery (min), median (25th–75th percentile)	179 (140–222)	181 (146–221)
Time in operation room (min), median (25th–75th percentile)	293 (249–339)	297 (251–341)

NT narcotrend, *OPCAB* off-pump coronary artery bypass grafting, *CPB* cardiopulmonary bypass

towards light anesthesia before incision (see Fig. 3) as the possible timeframe of the awareness event. Seven patients, solely restricted to the control group, died in the hospital due to multiorgan failure (n = 3), cardiogenic shock (n = 2) or respiratory failure (n = 2). The study intervention was not related with death in any case. Detailed results of secondary endpoints are displayed in Table 3.

4 Discussion

The results of the present trial can be summarized as follows: (I) With use of pEEG vasopressor dosage can significantly be reduced in patients undergoing elective cardiac surgery. However, the observed reduction was lower in absolute and relative terms than the postulated clinically

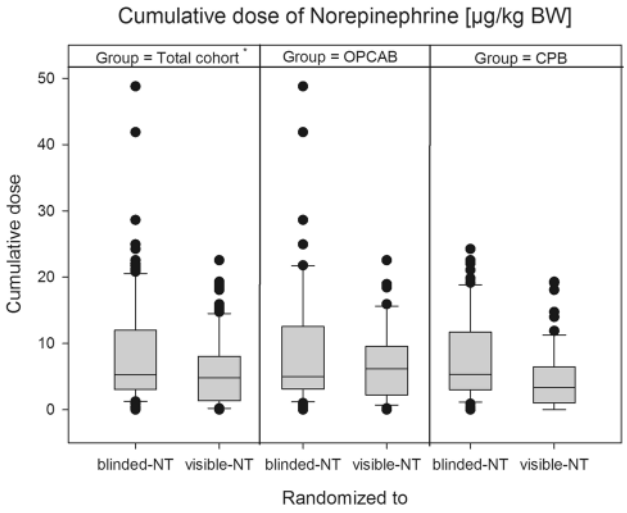

Fig. 2 Boxplot of cumulative dose of Norepinephrine [µg/kg body weight] as the primary endpoint; data below the 10th or above the 90th percentile are shown as single dots (*OPCAB* off-pump coronary artery bypass grafting, *CPB* cardiopulmonary bypass). *p < 0.05

relevant effect size. (II) The use of pEEG has no influence on perioperative fluid balance and risk of delirium. (III) Adverse events as intraoperative movement, breathing or perspiration might occur despite low NI, while high NI may be associated with higher incidence of hypertension.

Hypotension within general anesthesia is frequent. Independent predictors of hypotension are older age, propofol administration in combination of high doses of opioid analgesics, low baseline blood pressure and higher grade in ASA classification [20]. In cardiac surgery patients, low systemic vascular resistance on CPB [21] presents another reason for hypotensive episodes. Use of vasopressors or fluid administration are common strategies to counteract low MAP [15]. However, use of inotropes (i.e. dobutamine) or vasopressors (i.e. norepinephrine) were also associated with adverse events and deterioration of poor outcome especially in cardiac surgical patients [3]. Thus, strategies reducing hypotensive episodes and use of vasopressors may reduce adverse events (i.e. renal failure) and preserve outcome. In the current trial, we were able to prevent cardiovascular compromise as reflected in reduced

Table 3 Primary and secondary endpoint results by intervention and type of surgery

	OPCAB n = 56	Blinded-NT[a] CPB n = 67	Total n = 123	OPCAB n = 57	Visible-NT[a] CPB n = 65	Total n = 122	Total effect (95% CI)	p-value
Primary endpoint								
Intraoperative norepinephrine (µg/kg)	4.86 (3.11–12.55)	5.23 (2.94–11.46)	5.08 (3.05–11.94)	6.14 (2.26–9.10)	3.34 (1.04–6.48)	4.73 (1.32–7.99)		
Robust location estimator	**6.49**[b]	**6.01**[b]	**6.14**[b]	**6.00**[b]	**3.52**[b]	**4.71**[b]	**1.71 (0.33, 3.10)**[c]	**0.015**
Missing data	*0*	*4*	*4*	*0*	*2*	*2*		
Secondary endpoints								
Perioperative crystalloid fluid (ml)	6626 (5000–7502)	5094 (3644–6511)	5801 (4250–7200)	6300 (5000–7500)	4787 (3841–6074)	5442 (4500–7200)	109 (−462, 671)[d]	0.710
Missing data	*0*	*4*	*4*	*0*	*3*	*3*		
Postoperative mechanical ventilation time (min)	270 (233–430)	345 (245–510)	305 (235–470)	270 (215–335)	280 (210–420)	275 (210–390)	40 (0, 75)[d]	0.062
Postoperative delirium	8/55 (14.5)	12/62 (19.4)	20/117 (17.1)	4/57 (7.0)	15/65 (23.1)	19/122 (15.6)	0.91 (0.51, 1.62)[e]	0.751
Missing data	*1*	*5*	*6*	*0*	*0*	*0*		

NT narcotrend, *OPCAB* off-pump coronary artery bypass grafting, *CPB* cardiopulmonary bypass, *CI* confidence interval

[a]Unless otherwise stated: Median (25th–75th percentile) for continuous data, count (%) for categorical data

[b]Huber-M-estimator of central tendency

[c]Location difference (*blinded-visible*) estimated by robust linear regression (Huber-M-estimator) and adjusted for type of bypass surgery

[d]Median of all possible *nblinded times nvisible* differences (*blindedi - visiblej*) for i = 1 to nblinded and j = 1 to nvisible

[e]Relative risk (visible/blinded)

Table 4 Proportion of patients receiving vasoactive medication and catecholamines during surgery to maintain the mean arterial blood pressure between 65 and 85 mmHg

	Blinded-NT n = 123	Visible-NT n = 122	p-value
Bolus injection, n (%)			
Ephedrine	28 (22.8)	23 (18.9)	0.451
Milrinone	10 (8.1)	8 (6.6)	0.637
Epinephrine	5 (4.1)	2 (1.6)	0.254
Vasopressin	1 (0.8)	0 (0.0)	0.318
Urapidil	20 (16.3)	35 (28.7)	0.020
Nitroglycerine	0 (0.0)	3 (2.5)	0.080
Continuous application, n (%)			
Milrinone	1 (0.8)	2 (1.6)	0.556
Epinephrine	2 (1.6)	4 (3.3)	0.403

use of norepinephrine to maintain MAP between 65 and 85 mmHg in elective cardiac surgical patients by using NT. This effect was primarily attributable to the subset of patients undergoing on-pump surgery. The most likely explanation for vasopressor reduction in our trial is providing individualized depth of anesthesia, preserving vasotonus to react on hypotension and surgical stimuli. As shown before, individualization of anesthetic drug delivery using pEEG resulted in less anesthetic dose application, but did not alter surgical stress response in patients undergoing elective CABG surgery [22]. The finding of reduced vasopressor dosage using pEEG was shown before, however, not as primary study endpoint. Nitzschke et al. reported on significant norepinephrine reduction with bispectral index (BIS) in CABG patients [14]. In the study of Lehmann et al. CABG patients were allocated to either low (35–44) or high (45–55) BIS. In the low BIS group patients were more dependent from inotropic support [13]. Patients in the visible-NT group more often required bolus application of vasodilative agents (i.e. urapidil or nitroglycerine) especially during surgical preparation pre CPB or the aortic cannulation process, were systolic blood pressure should not exceed 100 mmHg. As the concept of individualized anesthetic drug administration aims to preserve the sympathetic response to surgical, commonly non-painful stimuli (such as the aortic cannulation process), application of vasodilative agents to lower the MAP in this situations may be reasonable. Taken together, pEEG controlled anesthesia in patients undergoing elective cardiac surgery seemingly reduced vasopressors by providing individualized and optimized anesthetic drug administration.

Studies focusing on volume requirements of individualized anesthetic drug delivery using pEEG monitoring are lacking. Both, overhydration with central and peripheral edema and fluid restriction with postoperative shock or renal failure are associated with perioperative morbidity [23]. Specifically reduced vasopressor use could result in fluid administration in order to maintain MAP ≥ 65 mmHg. We therefore monitored perioperative fluid administration and observed similar volumes applied in both groups. This supports the hypothesis that maintained vascular tone might lead to less vasopressors without altering fluid administration.

PEEG guided anesthesia was shown to shorten postoperative ventilation time in mixed surgical patients [24]. However, patients undergoing cardiac surgery may be prone to pulmonary complications in the postoperative period [25]. In the current trial intraoperative use of NT was associated with a non-significant reduction of postoperative extubation times. This is in accordance to a previous study, where intraoperative use of BIS did not alter postoperative extubation times [26]. Moreover, postoperative BIS also did not influence extubation times in patients

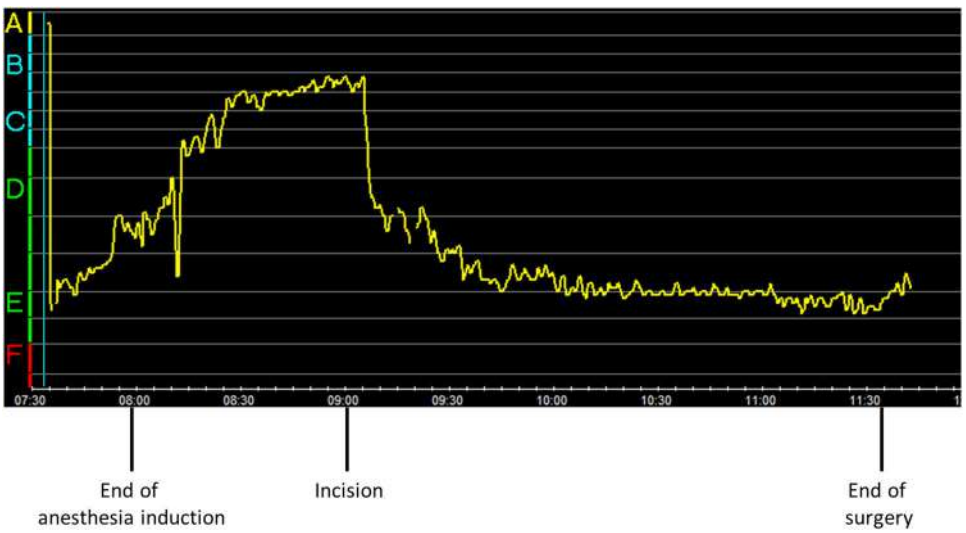

Fig. 3 Course of Narcotrend Index values (Cerebrogram) in the patient allocated to the blinded-NT group reporting on intraoperative awareness

following cardiac surgery [27]. Implementing special post anesthetic care units [28] and time directed extubation protocols [29] may allow safe and early extubation after cardiac surgery.

Postoperative delirium is common after cardiac surgery, affecting up to 50% of patients [30]. In the current trial we found similar rates of postoperative delirium among patients with visible-NT or blinded-NT. Regarding pEEG and occurrence of postoperative delirium after cardiac surgery Soehle et al. reported on longer duration times of burst suppression ratio in patients with delirium compared to those without [31]. However, as the current trial was not powered to evaluate postoperative delirium and the incidence of delirium was low in our patient cohort, we were not able to support previously reported beneficial effects of pEEG.

Recently, Cascella et al. reported a case of sudden arousal and movement in a patient undergoing major abdominal surgery, despite BIS < 50 and provided a critical discussion of measuring depth of anesthesia [32]. In the current trial we also realized adverse events represented by sudden movement/coughing/breathing, perspiration or hypertension despite "adequate" NI. As shown before, pEEG is not a good predictor of intraoperative movement [33, 34] as these are usually a cause of lower brain and spinal cord responses to nociceptive stimuli. Moreover, one patient in the current study reporting on possible intraoperative awareness was operated without visible-NT. Reviewing the literature reports on adverse events of pEEG are lacking and should be reported more frequently. On the other hand there is no doubt in reducing the risk of possible awareness in high risk patients and procedures (as cardiac surgery) using pEEG [24]. Finally, the use of pEEG is recommended by the German Society of anesthesiologists in patients undergoing cardiac surgery [35]. Furthermore, consensus exists in using pEEG monitoring in patients undergoing total intravenous anesthesia coupled with neuromuscular blockade, rather than in patients undergoing inhalational anesthesia [36]. In this respect, the choice of monitor might be secondary, when knowing the strength and limitations [10, 36] of the referring monitors. Taken together, the use of pEEG may provide patient safety by reducing the risk of intraoperative awareness, but also exerts limitations referring to neuromuscular blockage or other sedative medications (i.e.ketamine) [36].

One limitation of our trial is the single centre design. However, the one centre design allowed for direct effect comparison of pEEG, not biased by differences in anesthesiologic or surgical management. Another limitation represents the inclusion of patients operated on CPB as well as off-pump surgery. In OPCAB surgery, inflammatory components mediating hypotension of the CPB may be avoided. However, release of cytokines in off-pump surgery has been demonstrated as well [37]. Moreover, during OPCAB swings in blood pressure primarily through manipulating the heart may occur, making it difficult to compare vasopressor need in both patient groups. Nevertheless, pEEG might also provide benefits in reducing vasopressor support in this special patient cohort. This should, however, be evaluated in a larger clinical trial including only OPCAB patients. Owing to the unexpected distribution of the primary endpoint data we modified the planned analysis and used robust regression instead of nonparametric test statistics. This approach allowed including type of surgery as covariate to reduce variability and to explore subgroup effects by adding an interaction term to the model. Furthermore, we missed primary endpoint data due to logistic problems that were not related to the endpoint. Four out of 123 patients of the control group and two out of 122 patients of the visible-NT group were affected. In that case attrition bias seems unlikely. The inclusion of only elective cardiac surgery patients is another limitation. Emergency patients may also or even more profit from individualized anesthetic management using pEEG. Moreover, expanding the pEEG on postoperative ICU management would allow reducing vasopressor support in the postoperative phase, could lead to faster postoperative extubation and may reduce delirium. These hypotheses should be tested in independent trials.

Taken together, implementation of pEEG into the anesthesiologic management of elective cardiac surgery patients reduced the intraoperative need for vasopressor support. It needs to be further investigated if the subgroup of patients operated on CPB would benefit more from pEEG compared to OPCAB patients.

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Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest regarding this manuscript.

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