Journal of Clinical Anesthesia 95 (2024) 111459

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

Processed electroencephalography-guided general anesthesia and norepinephrine requirements: A randomized trial in patients having vascular surgery

Kristen K. Thomsen, M.D. [a,*], Daniel I. Sessler, M.D. [b], Linda Krause, PhD [c], Phillip Hoppe, M.D. [a], Benjamin Opitz, M.D. [a], Till Kessler, M.D. [a], Viorel Chindris, M.D. [a], Alina Bergholz, M.D. [a], Moritz Flick, M.D. [a], Karim Kouz, M.D. [a,d], Christian Zöllner, M.D. [a], Leonie Schulte-Uentrop, M.D. [a,1], Bernd Saugel, M.D. [a,d,1]

[a] Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[b] Outcomes Research Consortium, Department of Anesthesiology, Cleveland Clinic, Cleveland, OH, USA
[c] Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[d] Outcomes Research Consortium, Cleveland, OH, USA

HIGHLIGHTS

- To prevent and treat intraoperative hypotension, vasopressors are commonly used.
- Avoiding excessive depth of anesthesia may reduce the need for vasopressors.
- Processed electroencephalography helps avoid excessive anesthetic depth.
- Processed electroencephalography reduces norepinephrine requirements

ARTICLE INFO

Keywords:
Anesthesia
Hemodynamic monitoring
Blood pressure
Electroencephalography
Hypotension
Acute kidney injury
Vasopressor
Patient state index

ABSTRACT

Study Objective: Processed electroencephalography (pEEG) may help clinicians optimize depth of general anesthesia. Avoiding excessive depth of anesthesia may reduce intraoperative hypotension and the need for vasopressors. We tested the hypothesis that pEEG-guided – compared to non-pEEG-guided – general anesthesia reduces the amount of norepinephrine needed to keep intraoperative mean arterial pressure above 65 mmHg in patients having vascular surgery.
Design: Randomized controlled clinical trial.
Setting: University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
Patients: 110 patients having vascular surgery.
Interventions: pEEG-guided general anesthesia.
Measurements: Our primary endpoint was the average norepinephrine infusion rate from the beginning of induction of anesthesia until the end of surgery.
Main Result: 96 patients were analyzed. The mean ± standard deviation average norepinephrine infusion rate was 0.08 ± 0.04 μg kg^{-1} min^{-1} in patients assigned to pEEG-guided and 0.12 ± 0.09 μg kg^{-1} min^{-1} in patients assigned to non-pEEG-guided general anesthesia (mean difference 0.04 μg kg^{-1} min^{-1}, 95% confidence interval 0.01 to 0.07 μg kg^{-1} min^{-1}, $p = 0.004$). Patients assigned to pEEG-guided *versus* non-pEEG-guided general anesthesia, had a median time-weighted minimum alveolar concentration of 0.7 (0.6, 0.8) *versus* 0.8 (0.7, 0.8) (*p*

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; EEG, Electroencephalography; MAP, Mean arterial pressure; pEEG, Processed electroencephalography; PSi, Patient State Index; SEF95, 95% spectral edge frequency.

* Corresponding author at: Kristen Kei Thomsen, Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, Hamburg 20246, Germany.
E-mail address: science.thomsen@gmail.com (K.K. Thomsen).

[1] Leonie Schulte-Uentrop and Bernd Saugel contributed equally.

https://doi.org/10.1016/j.jclinane.2024.111459
Received 21 December 2023; Received in revised form 19 March 2024; Accepted 26 March 2024
Available online 9 April 2024

= 0.006) and a median percentage of time Patient State Index was <25 of 12 (1, 41) % *versus* 23 (3, 49) % (p = 0.279).

Conclusion: pEEG-guided – compared to non-pEEG-guided – general anesthesia reduced the amount of norepinephrine needed to keep mean arterial pressure above 65 mmHg by about a third in patients having vascular surgery. Whether reduced intraoperative norepinephrine requirements resulting from pEEG-guided general anesthesia translate into improved patient-centered outcomes remains to be determined in larger trials.

1. Introduction

Hypotension is common during surgery with general anesthesia and is associated with postoperative organ injury [1–5]. To prevent and treat intraoperative hypotension, vasopressors such as norepinephrine are commonly used. However, vasopressors themselves may promote acute kidney injury [6–8].

One factor that contributes to intraoperative hypotension, and thus vasopressor requirements, is deep general anesthesia. Processed electroencephalography (pEEG) may help clinicians optimize depth of general anesthesia [9–11]. Avoiding excessive depth of anesthesia may, in turn, reduce intraoperative hypotension and the need for vasopressors.

We therefore aimed to determine whether pEEG-guided general anesthesia reduces norepinephrine requirements. Specifically, we tested the primary hypothesis that pEEG-guided – compared to non-pEEG-guided – general anesthesia reduces the amount of norepinephrine needed to keep intraoperative mean arterial pressure (MAP) above 65 mmHg in patients having vascular surgery.

2. Materials and methods

2.1. Study design and setting

Patients were enrolled in the Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf between February 2022 and March 2023. The trial was approved by the ethics committee (Ethikkommission der Ärztekammer Hamburg, Hamburg, Germany; Chairperson Prof. R. Stahl; registration number 2020–10155-BO-ff) on February 16, 2021 and registered at ClinicalTrials.gov (NCT05293288) on March 23, 2022. Participating patients provided written informed consent. We report the trial according to the Consolidated Standards of Reporting Trials (CONSORT) statement [12].

2.2. Patient selection

We included consenting patients ≥45 years old who were scheduled for elective vascular surgery with general anesthesia when: a) surgery was expected to last at least an hour; b) estimated intraoperative blood loss was <1000 mL; and c) intra-arterial blood pressure monitoring with an arterial catheter was planned. We excluded patients who had previous solid organ transplants; were septic; were designated American Society of Anesthesiologists physical status V or VI; or were pregnant. After randomization, we further excluded patients who were given other vasopressors besides norepinephrine during surgery.

2.3. Protocol

We used pEEG from induction of general anesthesia until the end of surgery. Specifically, we used the SedLine Brain Function Monitor (Masimo, Irvine, CA, USA) which displays 4 raw electroencephalography (EEG) tracings, the Patient State Index (PSi), density spectral arrays, and the 95% spectral edge frequency (SEF95). The raw frontal and pre-frontal EEG tracings are further processed into the unitless PSi, ranging from 0 to 100, through a proprietary algorithm (0 = isoelectric EEG, 100 = EEG of an awake person) [13]. Density spectral arrays show the EEG power across different frequencies over time [9]. The SEF95 stands for the frequency below which 95% of the total EEG power is located [9]. Additionally, the monitor displays a variable reflecting the amount of noise contaminating the EEG signal in percent and electromyographic activity (a measure of muscular activity contaminating the EEG signal). Data from the pEEG monitor were recorded and extracted at 2-s intervals using the Masimo Instrument Configuration Tool Software (Masimo).

Patients were randomized to pEEG-guided general anesthesia or to non-pEEG-guided general anesthesia (with blinded pEEG monitoring) in a 1:1 ratio without blocking or stratification based on computer-generated codes. Group allocation was concealed in sequentially numbered opaque envelopes that were opened shortly before anesthetic induction. Patients were blinded to group allocation, but anesthesiologists could not be.

In both groups, general anesthesia was induced using an opioid (sufentanil bolus or continuous remifentanil infusion), propofol, and rocuronium or cisatracurium. Patients' lungs were mechanically ventilated *via* an endotracheal tube or laryngeal mask. General anesthesia was maintained with either inhaled sevoflurane or a continuous propofol infusion, with repeated boluses of sufentanil or continuous remifentanil as clinically indicated. Patients were given balanced electrolyte solution (Sterofundin ISO; Braun, Melsungen, Germany) as baseline fluid infusion. Additional fluids were given at the discretion of the treating anesthesiologists.

Clinicians strove to keep MAP above 65 mmHg using continuous norepinephrine infusion per institutional routine. Norepinephrine was continuously given *via* syringe infusion pumps (Perfusor Space; B Braun, Melsungen, Germany) using 50 mL syringes containing 3 mg norepinephrine diluted with normal saline 0.9% to 50 mL. Blood pressure was measured with a radial arterial catheter in most patients, and otherwise with upper-arm cuff oscillometry when planned arterial catheters were not inserted for clinical reasons. Arterial catheters were inserted either before or after anesthetic induction. Blood pressures were extracted from electronic anesthesia records.

In patients assigned to pEEG-guided general anesthesia, depth of anesthesia was adjusted to the pEEG, specifically considering PSi and SEF95 values. In case of contradictory PSi and SEF95 values, noise contamination, electromyography, and the overall clinical situation informed clinical decisions regarding general anesthesia. Otherwise, there was no specific treatment algorithm for pEEG-guided general anesthesia. In patients assigned to non-pEEG-guided general anesthesia (with blinded pEEG monitoring), depth of general anesthesia management was based on clinical judgment informed by clinical perception, vital signs, and anesthetic dosing.

2.4. Endpoints

Our primary endpoint was the average norepinephrine infusion rate in μg per kg actual body weight per minute (μg kg^{-1} min^{-1}) from the beginning of induction of general anesthesia until the end of surgery. Total amounts of norepinephrine were extracted from syringe infusion pumps at the end of surgery.

Secondary endpoints quantifying intraoperative hypotension were the cumulative time with a MAP <65 mmHg and time-weighted average MAP <65 mmHg (area under a MAP of 65 mmHg divided by the time from the beginning of induction of general anesthesia until the end of

surgery). The area under a MAP of 65 mmHg was calculated by subtracting MAP measurements from 65 mmHg, multiplying positive differences with the time difference (in minutes) between this MAP measurement and the consecutive MAP measurement, and summing the values.

On a *post hoc* basis, we evaluated the median PSi; the median percentage of time PSi was <25; the median SEF95; the median percentage of time SEF95 was <8 Hz; the median percentage of time with a suppression ratio >0%; the median percentage of time with a suppression ratio >5%; the median cumulative minutes with a suppression ratio >0%; the median cumulative minutes with a suppression ratio >5%; the percentage of total monitoring time patients had a suppression ratio of >0%; and the percentage of total monitoring time patients had a suppression ratio of >5%. We additionally calculated the median time-weighted minimum alveolar concentration (MAC) in patients in whom general anesthesia was maintained with inhaled sevoflurane.

2.5. Statistical analysis

The statistical analysis plan was approved by the principal investigators and trial statistician before data analysis. Patients' demographic, baseline, and clinical characteristics are described separately for patients assigned to pEEG-guided and non-pEEG-guided general anesthesia. Categorical data are presented as absolute numbers (percentages). Continuous data are presented as means ± standard deviations (normally distributed data) or medians (25th percentile, 75th percentile) (non-normally distributed data). The primary endpoint was analyzed using a two-sided two-sample *t*-test. We performed *post hoc* sensitivity analyses a) restricted to patients in whom general anesthesia was maintained with inhaled sevoflurane and b) restricted to patients who had intra-arterial blood pressure monitoring with an arterial catheter. Continuous secondary endpoints were analyzed using Wilcoxon rank sum tests with continuity correction.

We estimated the sample size needed for our primary endpoint. Assuming that the standard deviation of the average norepinephrine infusion rate is 0.06 μg kg^{-1} min^{-1}, a sample size of 48 patients per group (n = 96 patients in total) would provide 90% power at a 0.05 significance level to detect a difference in the average norepinephrine infusion rate between the two groups of 0.04 μg kg^{-1} min^{-1} or larger. We expected a drop-out rate of 15% (largely related to the use of other vasopressors besides norepinephrine), and thus planned to include 110 patients (55 patients per group).

3. Results

As planned, we randomized 110 patients between February 22, 2022, and March 2, 2023. After randomization, we excluded 13 patients because other vasopressors besides norepinephrine were used and one patient because surgery was cancelled. We thus finally analyzed 96 patients – 48 patients (50%) assigned to pEEG-guided general anesthesia and 48 patients (50%) assigned to non-pEEG-guided general anesthesia (Fig. 1). Patient characteristics and procedural data are shown in Table 1.

The mean ± standard deviation average norepinephrine infusion rate was 0.08 ± 0.04 μg kg^{-1} min^{-1} in patients assigned to pEEG-guided and 0.12 ± 0.09 μg kg^{-1} min^{-1} in patients assigned to non-pEEG-guided general anesthesia (mean difference 0.04 μg kg^{-1} min^{-1}, 95% confidence interval 0.01 to 0.07 μg kg^{-1} min^{-1}, p = 0.004) (Fig. 2).

In 86 of the 96 patients (90%) general anesthesia was maintained with inhaled sevoflurane. In these patients, the mean ± standard

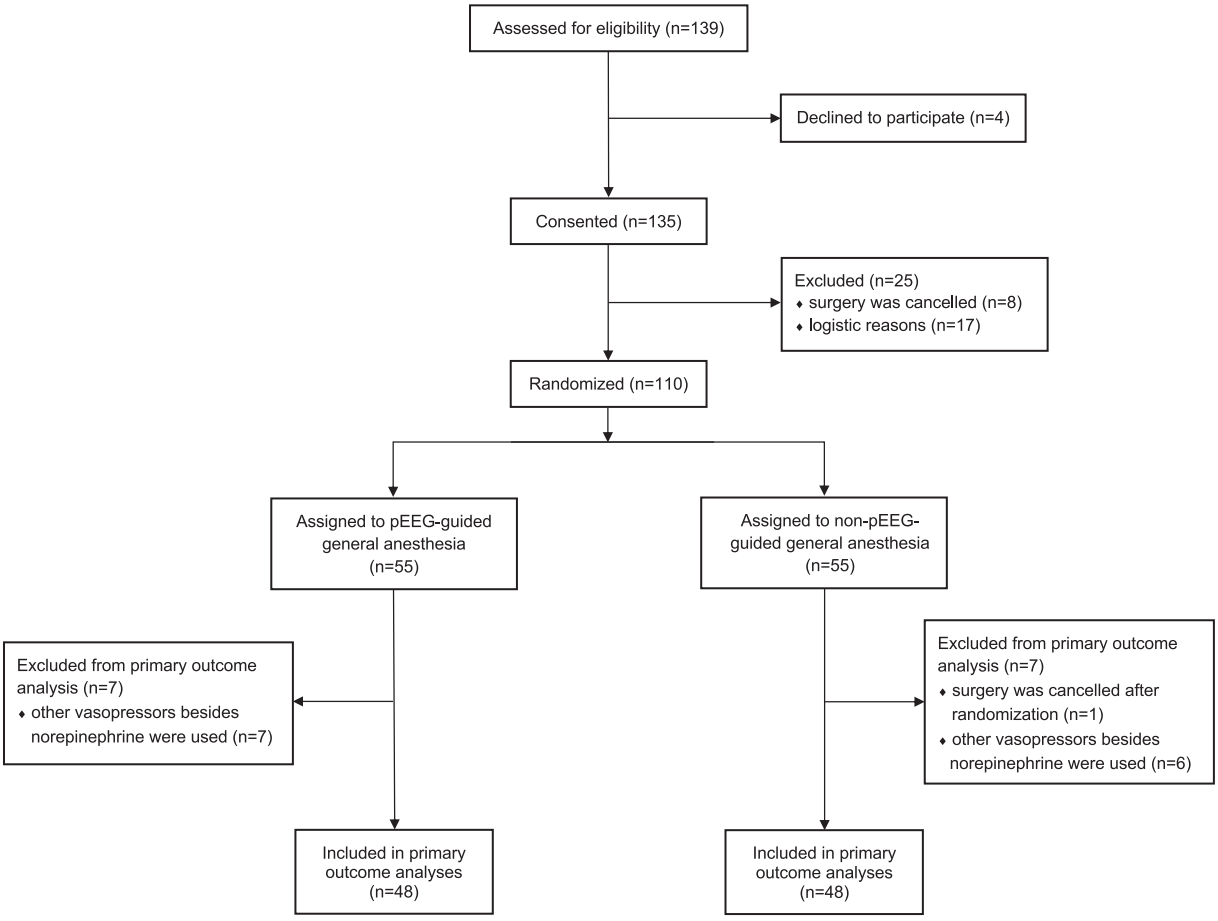

Fig. 1. Flow chart illustrating randomization and reasons for exclusion.

Table 1
Patient characteristics and procedural data.

	pEEG-guided general anesthesia (n = 48)	Non-pEEG-guided general anesthesia (n = 48)	Absolute standardized differences
Age, years	75 (70, 78)	74 (69, 82)	0.031
Body mass index, kg m^{-2}	26 (23, 28)	25 (23, 29)	0.007
Sex			0.177
Male, n	34 (71)	30 (63)	
Female, n	14 (29)	18 (38)	
Type of surgery			0.306
Carotid-subclavian bypass, n	1 (2)	2 (4)	
Carotid endarterectomy, n	2 (4)	1 (2)	
Endovascular aortic repair, n	16 (33)	15 (31)	
Percutaneous transluminal angioplasty, n	1 (2)	3 (6)	
Peripheral vascular surgery, n	22 (46)	23 (48)	
Thoracic endovascular aortic repair, n	4 (8)	3 (6)	
Transcaval coil embolization, n	2 (4)	1 (2)	
Anesthetic management			
Time from the beginning of induction of general anesthesia until the end of surgery, min	215 (150, 313)	229 (162, 313)	0.165
General anesthesia with sevoflurane, n	43 (90)	43 (90)	0.065
General anesthesia with propofol, n	5 (10)	5 (10)	
Total volume of crystalloid and colloidal fluids, mL	1500 (1500, 2500)	1900 (1250, 3000)	0.042
Patients with allogenic (packed red blood cells) or autologous (cell salvage) transfusion, n	9 (19)	11 (23)	0.103
Volume of transfused red blood cells (allogenic and autologous), mL	1100 (350, 1200)	500 (300, 1050)	0.069

Categorical data are presented as absolute number (percentage), continuous data as median (25th percentile, 75th percentile). Percentages may not sum up to 100% due to rounding. n, absolute number. pEEG: processed electroencephalography.

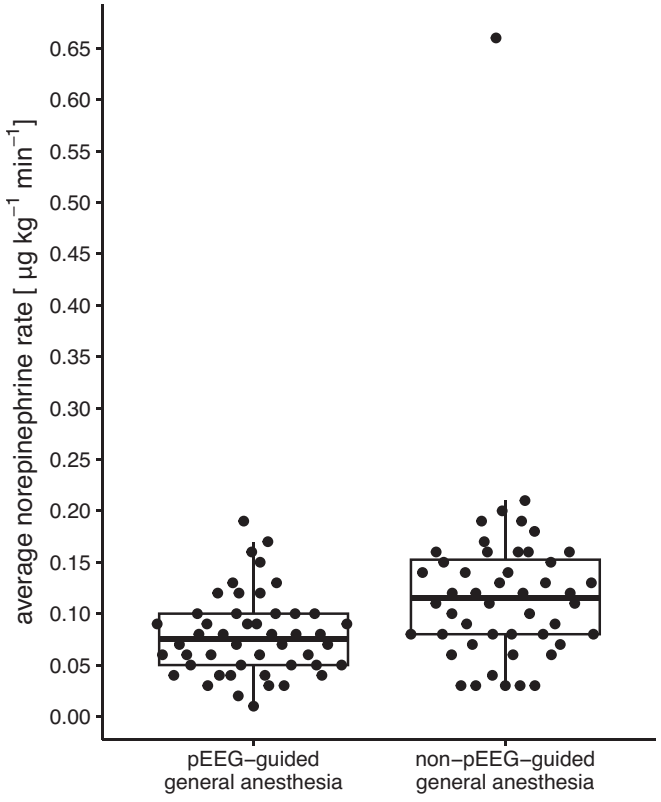

Fig. 2. Boxplots with overlying one-dimensional scatter plot showing the average norepinephrine infusion rates in patients assigned to pEEG-guided and non-pEEG-guided general anesthesia. Boxes represent the 25th and 75th percentile and the range between them is the interquartile range. Inside the boxes, bold horizontal lines represent medians. The whiskers (extensions from the box) indicate the lowest and highest value no further than 1.5 times the interquartile range.

deviation average norepinephrine infusion rate was 0.08 ± 0.04 µg kg^{-1} min^{-1} in patients assigned to pEEG-guided and 0.13 ± 0.10 µg kg^{-1} min^{-1} in patients assigned to non-pEEG-guided general anesthesia (mean difference 0.04 µg kg^{-1} min^{-1}, 95% confidence interval 0.01 to 0.08 µg kg^{-1} min^{-1}, $p = 0.007$).

91 of the 96 patients (95%) had intra-arterial blood pressure monitoring with an arterial catheter. In these patients, the mean ± standard deviation average norepinephrine infusion rate was 0.08 ± 0.04 µg kg^{-1} min^{-1} in patients assigned to pEEG-guided and 0.13 ± 0.10 µg kg^{-1} min^{-1} in patients assigned to non-pEEG-guided general anesthesia (mean difference 0.05 µg kg^{-1} min^{-1}, 95% confidence interval 0.02 to 0.08 µg kg^{-1} min^{-1}, $p = 0.003$).

The median (25th percentile, 75th percentile) percentage of time PSi was <25 was 12 (1, 41) % in patients assigned to pEEG-guided general anesthesia and 23 (3, 49) % in patients assigned to non-pEEG-guided general anesthesia ($p = 0.279$) (Table 2). The median (25th percentile, 75th percentile) percentage of time with a suppression ratio >5% was 1 (0, 11) % in patients assigned to pEEG-guided general anesthesia and 4 (0, 29) % in patients assigned to non-pEEG-guided general anesthesia ($p = 0.095$) (Table 2). The percentage of total monitoring time patients had a suppression ratio of >5% was 8% in patients assigned to pEEG-guided general anesthesia and 19% in patients assigned to non-pEEG-guided general anesthesia. In the 86 patients in whom general anesthesia was maintained with inhaled sevoflurane, the median (25th percentile, 75th percentile) time-weighted MAC was 0.7 (0.6, 0.8) in patients assigned to pEEG-guided general anesthesia and 0.8 (0.7, 0.8) in patients assigned to non-pEEG-guided general anesthesia ($p = 0.006$).

The median (25th percentile, 75th percentile) time-weighted average MAP <65 mmHg was 0.34 (0.09, 0.67) mmHg in patients assigned to pEEG-guided and 0.18 (0.01, 0.69) mmHg in patients assigned to non-pEEG-guided general anesthesia ($p = 0.224$) – with a median (25th percentile, 75th percentile) cumulative time with a MAP <65 mmHg of 15 (7, 25) minutes and 10 (3, 29) minutes ($p = 0.408$).

4. Discussion

pEEG-guided – compared to non-pEEG-guided – general anesthesia

Table 2
Intraoperative processed electroencephalography data.

	pEEG-guided general anesthesia ($n = 42$)	Non-pEEG-guided general anesthesia ($n = 46$)	*P*-values
Patient State Index	32 (25, 36)	30 (24, 34)	0.323
Percentage of time with patient state index <25, %	12 (1, 41)	23 (3, 49)	0.279
Spectral edge frequency 95%, Hz	11 (8, 14)	10 (8, 12)	0.304
Percentage of time with spectral edge frequency 95% <8 Hz, %	8 (2, 46)	15 (4, 43)	0.365
Percentage of time with a suppression ratio >0%, %	3 (0, 18)	7 (2, 38)	0.047
Percentage of time with a suppression ratio >5%, %	1 (0, 11)	4 (0, 29)	0.095
Cumulative minutes with a suppression ratio >0%, min	5 (1, 32)	13 (2, 94)	0.052
Cumulative minutes with a suppression ratio >5%, min	1 (0, 15)	5 (0, 63)	0.068
Percentage of total monitoring time patients had a suppression ratio of >0%, %	14	27	n.a.
Percentage of total monitoring time patients had a suppression ratio of >5%, %	8	19	n.a.

Continuous data, if applicable, are presented as median (25th percentile, 75th percentile).
pEEG: processed electroencephalography.

reduced the amount of norepinephrine needed to keep intraoperative MAP above 65 mmHg by about a third, a reduction that was both statistically significant and clinically meaningful. Presumably, less norepinephrine was required with pEEG-guidance because anesthesia was lighter, thus reducing hypotension consequent to anesthetic drugs [14,15]. Consistent with this assumption, the median percentage of time PSi was <25 and the median percentage of time with a suppression ratio >5% was substantially lower in patients assigned to pEEG-guided – compared to non-pEEG-guided – general anesthesia.

Our results in non-cardiac surgery patients are consistent with those reported in 225 cardiac surgery patients in whom pEEG-guided anesthetic management reduced the cumulative norepinephrine dose required to maintain MAP between 65 and 85 mmHg by about a quarter compared to routine care [16]. Patients in the cardiac surgery trial were given less norepinephrine than our vascular surgery patients, but –complicating interpretation – most were also given other vasopressors whereas our analysis was restricted to patients who were only given norepinephrine. The effect of pEEG-guided anesthetic management on norepinephrine use was nonetheless similar in both trials, suggesting a generalizable benefit.

Although trial evidence is equivocal [17–19], there is now compelling evidence from observational research that intraoperative hypotension is associated with acute kidney injury [3,4,20–22], myocardial injury [3,4,23,24], and death [4]. As a result, there is a growing consensus that intraoperative hypotension should be avoided and that intraoperative MAP should be kept above 60–65 mmHg [25,26]. Therefore, clinicians in our institution routinely strive to keep MAP above 65 mmHg.

The duration and severity of intraoperative hypotension indeed did not substantially differ between patients assigned to pEEG-guided and non-pEEG-guided general anesthesia: the median time-weighted average MAP <65 mmHg was 0.34 *versus* 0.18 mmHg in patients assigned to pEEG-guided and non-pEEG-guided general anesthesia – a difference that, for example, would result when the MAP was 58 *versus* 61 mmHg for 10 minutes or when the MAP was 60 mmHg for 15 *versus* 10 minutes during the entire monitoring time (>3.5 h in both groups). Norepinephrine thus largely prevented hypotension in both groups, thereby justifying a comparison between norepinephrine infusion rates.

Observational studies suggest that vasopressors themselves are associated with acute kidney injury [6–8]. It thus seems prudent to both avoid profound hypotension and minimize vasopressor requirements. In our trial, the mean difference in the average norepinephrine infusion rate between patients assigned to pEEG-guided and non-pEEG-guided general anesthesia was 0.04 μg kg^{-1} min^{-1}. In one predictive model, an increase in use of norepinephrine equivalents from 0 to 0.04 μg kg^{-1} min^{-1} was associated with nearly twice as much acute kidney injury [6]. In our trial, pEEG helped clinicians spare norepinephrine. However, the trial was not powered to determine whether sparing norepinephrine by using pEEG translates into a reduction in postoperative complications.

In our trial, pEEG-guidance resulted in substantially less time patients had a suppression ratio of >0% and >5%. Burst suppression EEG pattern is a non-specific and non-physiological sign of suppressed brain activity and mainly has been attributed to a relative "overdose" of anesthetics [27,28], but may also be linked to cerebral hypoperfusion during intraoperative hypotension [29,30]. Intraoperative EEG burst suppression is associated with postoperative delirium [28,31,32] and mortality [33] – and should thus be avoided. Independent risk factors for the development of burst suppression include older age, male sex, chronic artery disease, and comorbidities [34,35] – typical characteristics of vascular surgery patients who might therefore particularly benefit from pEEG monitoring.

pEEG monitors generate quantitative indices based on proprietary algorithms to help clinicians optimize depth of anesthesia. pEEG indices are easier to use than raw EEG signals, but may underestimate burst suppressions [36,37], incorrectly estimate hypnotic state [38,39], and be influenced by artifacts [40].

A specific limitation of our single-center trial is that it was restricted to high-risk vascular surgery patients who were at least 45 years old. It thus focused on patients most at risk for hypotension-induced organ injury [41–43]. Our findings can nonetheless presumably be generalized to patients having other types of major non-cardiac surgery, especially those at substantial cardiovascular risk. Our anesthesiologists were well-trained in using pEEG monitoring. Both pEEG-guided general anesthesia and hemodynamic management were at clinicians' discretion. Especially, we did not use a specific treatment algorithm for pEEG-guided general anesthesia. Possibly using a specific treatment protocol for pEEG-guided general anesthesia would have helped further reduce norepinephrine requirements.

In conclusion, pEEG-guided – compared to non-pEEG-guided – general anesthesia reduced the amount of norepinephrine needed to keep intraoperative MAP above 65 mmHg by about a third in patients having vascular surgery. Whether reduced intraoperative norepinephrine requirements resulting from pEEG-guided general anesthesia translate into an improvement of patient-centered outcomes remains to be determined in larger trials. Our results suggest that such trials are warranted.

Disclosures

Support was provided solely from institutional and/or departmental sources.

Prior presentations

The trial was presented in the "Best of Abstracts: Clinical Science" session at the ANESTHESIOLOGY 2023 Annual Meeting, San Francisco, CA, USA (October 2023).

CRediT authorship contribution statement

Kristen K. Thomsen: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Conceptualization. **Daniel I. Sessler:** Writing – review & editing. **Linda Krause:** Writing – review & editing, Formal analysis, Data curation. **Phillip Hoppe:** Writing – review & editing, Formal analysis. **Benjamin Opitz:** Writing – review & editing. **Till Kessler:** Writing – review & editing. **Viorel Chindris:** Writing – review & editing. **Alina Bergholz:** Writing – review & editing. **Moritz Flick:** Writing – review & editing. **Karim Kouz:** Writing – review & editing. **Christian Zöllner:** Writing – review & editing. **Leonie Schulte-Uentrop:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Bernd Saugel:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: KKT has no conflicts of interest to declare. DIS has received research funding from Edwards Lifesciences; he also is an advisor and has equity interest in Perceptive Medical (Newport Beach, CA, USA). LK has no conflicts of interest to declare. PH has no conflicts of interest to declare. BO has no conflicts of interest to declare. TK has no conflicts of interest to declare. VC has no conflicts of interest to declare. AB has no conflicts of interest to declare. MF is a consultant for Edwards Lifesciences (Irvine, CA, USA) and has received honoraria for consulting and giving lectures from CNSystems Medizintechnik (Graz, Austria). KK is a consultant for and has received honoraria for giving lectures from Edwards Lifesciences (Irvine, CA, USA). KK is a consultand for Vygon (Aachen, Germany). CZ has no conflict of interest to declare. LS-U has no conflicts of interest to declare. BS has received honoraria for giving lectures from Masimo (Neuchâtel, Switzerland). BS is a consultant for and has received institutional restricted research grants and honoraria for giving lectures from Edwards Lifesciences (Irvine, CA, USA). BS is a consultant for Philips North America (Cambridge, MA, USA) and has received honoraria for giving lectures from Philips Medizin Systeme Böblingen (Böblingen, Germany). BS has received institutional restricted research grants and honoraria for giving lectures from Baxter (Deerfield, IL, USA). BS is a consultant for and has received institutional restricted research grants and honoraria for giving lectures from GE Healthcare (Chicago, IL, USA). BS has received institutional restricted research grants and honoraria for giving lectures from CNSystems Medizintechnik (Graz, Austria). BS is a consultant for Maquet Critical Care (Solna, Sweden). BS has received honoraria for giving lectures from Getinge (Gothenburg, Sweden). BS is a consultant for and has received institutional restricted research grants and honoraria for giving lectures from Pulsion Medical Systems (Feldkirchen, Germany). BS is a consultant for and has received institutional restricted research grants and honoraria for giving lectures from Vygon (Aachen, Germany). BS is a consultant for and has received institutional restricted research grants from Retia Medical (Valhalla, NY, USA). BS is a consultant for Dynocardia (Cambridge, MA, USA). BS has received institutional restricted research grants from Osypka Medical (Berlin, Germany). BS was a consultant for and has received institutional restricted research grants from Tensys Medical (San Diego, CA, USA). BS is an Editor of the British Journal of Anesthesia.

References

[1] Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology 2013;119:507–15. https://doi.org/10.1097/ALN.0b013e3182a10e26.

[2] Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. Anesthesiology 2017;126:47–65. https://doi.org/10.1097/ALN.0000000000001432.

[3] Ahuja S, Mascha EJ, Yang D, Maheshwari K, Cohen B, Khanna AK, et al. Associations of intraoperative radial arterial systolic, diastolic, mean, and pulse pressures with myocardial and acute kidney injury after noncardiac surgery: a retrospective cohort analysis. Anesthesiology 2020;132:291–306. https://doi.org/10.1097/ALN.0000000000003048.

[4] Gregory A, Stapelfeldt WH, Khanna AK, Smischney NJ, Boero IJ, Chen Q, et al. Intraoperative hypotension is associated with adverse clinical outcomes after noncardiac surgery. Anesth Analg 2021;132:1654–65. https://doi.org/10.1213/ANE.0000000000005250.

[5] Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth 2018;121:706–21. https://doi.org/10.1016/j.bja.2018.04.036.

[6] Chiu C, Fong N, Lazzareschi D, Mavrothalassitis O, Kothari R, Chen LL, et al. Fluids, vasopressors, and acute kidney injury after major abdominal surgery between 2015 and 2019: a multicentre retrospective analysis. Br J Anaesth 2022;129:317–26. https://doi.org/10.1016/j.bja.2022.05.002.

[7] Ariyarathna D, Bhonsle A, Nim J, Huang CKL, Wong GH, Sim N, et al. Intraoperative vasopressor use and early postoperative acute kidney injury in elderly patients undergoing elective noncardiac surgery. Ren Fail 2022;44:648–59. https://doi.org/10.1080/0886022X.2022.2061997.

[8] Zarbock A, Weiss R, Albert F, Rutledge K, Kellum JA, Bellomo R, et al. Epidemiology of surgery associated acute kidney injury (EPIS-AKI): a prospective international observational multi-center clinical study. Intensive Care Med 2023;49:1441–55. https://doi.org/10.1007/s00134-023-07169-7.

[9] Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical electroencephalography for anesthesiologists: part I: background and basic signatures. Anesthesiology 2015;123:937–60. https://doi.org/10.1097/ALN.0000000000000841.

[10] Chan MTV, Hedrick TL, Egan TD, Garcia PS, Koch S, Purdon PL, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on the role of Neuromonitoring in perioperative outcomes: electroencephalography. Anesth Analg 2020;130:1278–91. https://doi.org/10.1213/ANE.0000000000004502.

[11] Kreuzer M. EEG based monitoring of general anesthesia: taking the next steps. Front Comput Neurosci 2017;11:56. https://doi.org/10.3389/fncom.2017.00056.

[12] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Trials 2010;11:32. https://doi.org/10.1186/1745-6215-11-32.

[13] Prichep LS, Gugino LD, John ER, Chabot RJ, Howard B, Merkin H, et al. The patient state index as an indicator of the level of hypnosis under general anaesthesia. Br J Anaesth 2004;92:393–9. https://doi.org/10.1093/bja/aeh082.

[14] Saugel B, Bebert EJ, Briesenick L, Hoppe P, Greiwe G, Yang D, et al. Mechanisms contributing to hypotension after anesthetic induction with sufentanil, propofol, and rocuronium: a prospective observational study. J Clin Monit Comput 2022;36:341–7. https://doi.org/10.1007/s10877-021-00653-9.

[15] Kouz K, Brockmann L, Timmermann LM, Bergholz A, Flick M, Maheshwari K, et al. Endotypes of intraoperative hypotension during major abdominal surgery: a retrospective machine learning analysis of an observational cohort study. Br J Anaesth 2023;130:253–61. https://doi.org/10.1016/j.bja.2022.07.056.

[16] Sponholz C, Schuwirth C, Koenig L, Hoyer H, Coldewey SM, Schelenz C, et al. Intraoperative reduction of vasopressors using processed electroencephalographic monitoring in patients undergoing elective cardiac surgery: a randomized clinical trial. J Clin Monit Comput 2020;34:71–80. https://doi.org/10.1007/s10877-019-00284-1.

[17] Marcucci M, Painter TW, Conen D, Lomivorotov V, Sessler DI, Chan MTV, et al. Hypotension-avoidance versus hypertension-avoidance strategies in noncardiac surgery : an international randomized controlled trial. Ann Intern Med 2023;176:605–14. https://doi.org/10.7326/M22-3157.

[18] Wanner PM, Wulff DU, Djurdjevic M, Korte W, Schnider TW, Filipovic M. Targeting higher intraoperative blood pressures does not reduce adverse cardiovascular events following noncardiac surgery. J Am Coll Cardiol 2021;78:1753–64. https://doi.org/10.1016/j.jacc.2021.08.048.

[19] Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. Jama 2017;318:1346–57. https://doi.org/10.1001/jama.2017.14172.

[20] Tang Y, Zhu C, Liu J, Wang A, Duan K, Li B, et al. Association of Intraoperative Hypotension with acute kidney injury after noncardiac surgery in patients younger than 60 years old. Kidney Blood Press Res 2019;44:211–21. https://doi.org/10.1159/000498990.

[21] Mathis MR, Naik BI, Freundlich RE, Shanks AM, Heung M, Kim M, et al. Preoperative risk and the association between hypotension and postoperative acute kidney injury. Anesthesiology 2020;132:461–75. https://doi.org/10.1097/ALN.0000000000003063.

[22] Shaw AD, Khanna AK, Smischney NJ, Shenoy AV, Boero IJ, Bershad M, et al. Intraoperative hypotension is associated with persistent acute kidney disease after noncardiac surgery: a multicentre cohort study. Br J Anaesth 2022;129:13–21. https://doi.org/10.1016/j.bja.2022.03.027.

[23] Roshanov PS, Sheth T, Duceppe E, Tandon V, Bessissow A, Chan MTV, et al. Relationship between perioperative hypotension and perioperative cardiovascular events in patients with coronary artery disease undergoing major noncardiac surgery. Anesthesiology 2019;130:756–66. https://doi.org/10.1097/aln.0000000000002654.

[24] Hallqvist L, Granath F, Fored M, Bell M. Intraoperative hypotension and myocardial infarction development among high-risk patients undergoing noncardiac surgery: a nested case-control study. Anesth Analg 2021;133:6–15. https://doi.org/10.1213/ANE.0000000000005391.
[25] Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, et al. Perioperative quality initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 2019;122:563–74. https://doi.org/10.1016/j.bja.2019.01.013.
[26] Saugel B, Sessler DI. Perioperative blood pressure management. Anesthesiology 2021;134:250–61. https://doi.org/10.1097/ALN.0000000000003610.
[27] Bruhn J, Ropcke H, Rehberg B, Bouillon T, Hoeft A. Electroencephalogram approximate entropy correctly classifies the occurrence of burst suppression pattern as increasing anesthetic drug effect. Anesthesiology 2000;93:981–5. https://doi.org/10.1097/00000542-200010000-00018.
[28] Fritz BA, Kalarickal PL, Maybrier HR, Muench MR, Dearth D, Chen Y, et al. Intraoperative electroencephalogram suppression predicts postoperative delirium. Anesth Analg 2016;122:234–42. https://doi.org/10.1213/ANE.0000000000000989.
[29] Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, et al. Hospital stay and mortality are increased in patients having a “triple low” of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. Anesthesiology 2012;116:1195–203. https://doi.org/10.1097/ALN.0b013e31825683dc.
[30] Georgii MT, Kreuzer M, Fleischmann A, Schuessler J, Schneider G, Pilge S. Targeted interventions to increase blood pressure and decrease Anaesthetic concentrations reduce intraoperative burst suppression: A Randomised Interventional Clinical Trial. Front Syst Neurosci 2022;16:786816. https://doi.org/10.3389/fnsys.2022.786816.
[31] Radtke FM, Franck M, Lendner J, Kruger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013;110 (Suppl. 1):i98–105. https://doi.org/10.1093/bja/aet055.
[32] Soehle M, Dittmann A, Ellerkmann RK, Baumgarten G, Putensen C, Guenther U. Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. BMC Anesthesiol 2015;15:61. https://doi.org/10.1186/s12871-015-0051-7.
[33] Leslie K, Myles PS, Forbes A, Chan MT. The effect of bispectral index monitoring on long-term survival in the B-aware trial. Anesth Analg 2010;110:816–22. https://doi.org/10.1213/ANE.0b013e3181c3bfb2.
[34] Besch G, Liu N, Samain E, Pericard C, Boichut N, Mercier M, et al. Occurrence of and risk factors for electroencephalogram burst suppression during propofol-remifentanil anaesthesia. Br J Anaesth 2011;107:749–56. https://doi.org/10.1093/bja/aer235.
[35] Willingham M, Ben Abdallah A, Gradwohl S, Helsten D, Lin N, Villafranca A, et al. Association between intraoperative electroencephalographic suppression and postoperative mortality. Br J Anaesth 2014;113:1001–8. https://doi.org/10.1093/bja/aeu105.
[36] Muhlhofer WG, Zak R, Kamal T, Rizvi B, Sands LP, Yuan M, et al. Burst-suppression ratio underestimates absolute duration of electroencephalogram suppression compared with visual analysis of intraoperative electroencephalogram. Br J Anaesth 2017;118:755–61. https://doi.org/10.1093/bja/aex054.
[37] Fleischmann A, Georgii MT, Schuessler J, Schneider G, Pilge S, Kreuzer M. Always assess the raw electroencephalogram: why automated burst suppression detection may not detect all episodes. Anesth Analg 2023;136:346–54. https://doi.org/10.1213/ANE.0000000000006098.
[38] Ni K, Cooter M, Gupta DK, Thomas J, Hopkins TJ, Miller TE, et al. Paradox of age: older patients receive higher age-adjusted minimum alveolar concentration fractions of volatile anaesthetics yet display higher bispectral index values. Br J Anaesth 2019;123:288–97. https://doi.org/10.1016/j.bja.2019.05.040.
[39] Dahaba AA. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. Anesth Analg 2005;101:765–73. https://doi.org/10.1213/01.ane.0000167269.62966.af.
[40] Lobo FA, Schraag S. Limitations of anaesthesia depth monitoring. Curr Opin Anaesthesiol 2011;24:657–64. https://doi.org/10.1097/ACO.0b013e32834c7aba.
[41] Biccard BM, Scott DJA, Chan MTV, Archbold A, Wang CY, Sigamani A, et al. Myocardial injury after noncardiac surgery (MINS) in vascular surgical patients: a prospective observational cohort study. Ann Surg 2018;268:357–63. https://doi.org/10.1097/SLA.0000000000002290.
[42] Filiberto AC, Loftus TJ, Elder CT, Hensley S, Frantz A, Efron P, et al. Intraoperative hypotension and complications after vascular surgery: a scoping review. Surgery 2021;170:311–7. https://doi.org/10.1016/j.surg.2021.03.054.
[43] Rangasamy V, de Guerre L, Xu X, Schermerhorn ML, Novack V, Subramaniam B. Association between intraoperative hypotension and postoperative adverse outcomes in patients undergoing vascular surgery - a retrospective observational study. J Cardiothorac Vasc Anesth 2021;35:1431–8. https://doi.org/10.1053/j.jvca.2020.11.005.