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Pausing propofol during neurosurgery to record intraoperative electrocorticography is feasible;10 years of clinical experience

Dongqing Sun [a,1], Maryse A. van 't Klooster [a,1], Elise M. Ringeling [a], Eline V. Schaft [a], Peter C. van Rijen [a], Frans S.S. Leijten [a], Matteo Demuru [a], Pierre A.J.T. Robe [a], Reinier G. Hoff [b], Maeike Zijlmans [a,c,*], on behalf of the RESPect database group[a]

[a] Department of Neurology and Neurosurgery, UMC Utrecht Brain Center, Part of ERN EpiCARE, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, The Netherlands
[b] Department of Anesthesiology, Division of Anesthesiology, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, The Netherlands
[c] Stichting Epilepsie Instellingen Nederland (SEIN), Achterweg 2, 2103SW Heemstede, The Netherlands

HIGHLIGHTS

- Propofol administration can be paused to increase signal quality of ioECoG tailored epilepsy surgery.
- In our cohort of > 350 surgeries signs of inadequate sedation depth after temporarily pausing propofol administration were rare.
- Propofol administration was paused up to 30 min, though long pause durations were likely to induce hemodynamic changes.

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ABSTRACT

Objective: Intraoperative electrocorticography (ioECoG) during neurosurgery is influenced by anesthetics. In our center we stop the propofol to enable interpretation of ioECoG. We reported our clinical experience and evaluated awareness and hemodynamic changes during the propofol-free periods (PFP).
Methods: We retrospectively included surgeries with paused propofol administration to record ioECoG (period: 2008–2019). Clinical reports were screened for symptoms of awareness. We compared mean arterial blood pressure (MAP; mmHg) and heart rate (HR;bpm) during PFP to baseline (ten minutes preceding PFP). An increase > 15% was defined as clinically relevant. The association between hemodynamic changes and clinical characteristics was analyzed using logistic regression models.
Results: Propofol administration was paused 742 times in 352 surgeries (mean PFP duration 9 ± 5 min). No signs of awareness were reported. MAP and HR increased > 15% in 54 and six PFPs. Five PFPs showed both MAP and HR increases. Prolonged PFP was associated with having MAP and HR increase during surgery (OR=1.18, 95%CI [1.12–1.26]).
Conclusions: Signs of inadequate sedation depth were rare. MAP and HR increases were related to the length of PFP.
Significance: We summarize 10 years of clinical experience with pausing propofol administration during epilepsy surgery to record ioECoG without evidence of awareness.

1. Introduction

Epilepsy surgery is the only curative treatment for medically intractable epilepsy with a 36 to 84% chance to achieve postoperative seizure freedom (Englot et al., 2013, 2012; Schmidt and Stavem, 2009). Accurate resection of epileptogenic tissue is crucial to reach favorable seizure outcome. Electrophysiological biomarkers in intraoperative electrocorticography (ioECoG) can help to

* Corresponding author at: University Medical Center Utrecht and Stichting Epilepsie Instellingen Nederland (SEIN), The Netherlands.
E-mail address: g.j.m.zijlmans@umcutrecht.nl (M. Zijlmans).
[1] These authors contributed equally to this work.

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identify epileptogenic tissue and to improve the chance of seizure freedom (van Klink et al., 2021; Sun et al., 2020; van't Klooster et al., 2015). Optimal quality of the ioECoG signal is vital to interpret the epileptic biomarkers in order to guide the surgical plan (Zijlmans et al., 2012).

A common issue in ioECoG recording is the interaction of general anesthesia agents with the electrophysiological activity of the brain. All anesthetic agents may interfere with ioECoG background signals or alter the spatiotemporal characteristics of epileptic biomarkers in ways that can interfere with the interpretation of ioECoG. Some studies suggest that propofol has no significant effect on spikes but may reduce high-frequent oscillation rates (Kacar Bayram et al., 2021; Soriano et al., 2000; Zijlmans et al., 2012), while others show increased spike activity when using propofol (Dahaba et al., 2013). After propofol cessation, HFO levels increase and spike extent decreases over time. These levels stabilize at around 5 min (Zijlmans et al., 2012). Sevoflurane, on the other hand, may increase the occurrence of spikes and HFOs in epileptogenic tissue (Dahaba et al., 2013; Firestone et al., 2023; Kacar Bayram et al., 2021). Isoflurane is also associated with increased spikes rates in ioECoG (Kacar Bayram et al., 2021). Anesthetic drugs at low levels do not elicit electroencephalography (EEG) changes and the interruption of the administration of anesthetic drugs improves ioECoG signals.(Kacar Bayram et al., 2021) That is why some centers temporarily pause the administration of the anesthetic drugs during ioECoG recording (Peng et al., 2021; Sun et al., 2022; Wu et al., 2010).

Clinical guidelines do not yet exist for this procedure nor are there numbers on how many patients remain in adequate depth of sedation after pausing the administration of anesthetic drugs. A superficial level of anesthesia is a risk factor for awareness which may lead to depression, anxiety, and posttraumatic stress disorder (Hardman and Aitkenhead, 2005; Mashour et al., 2011). Pausing anesthesia administration during functional neurosurgery raises an important safety question; Will patients become unintendedly aware during surgery when propofol administration is paused? The University Medical Center Utrecht is amongst the biggest epilepsy surgery centers in Europe and specialized in ioECoG-assisted epilepsy surgery. We aimed to summarize 10 years of our clinical experience on the feasibility of pausing of propofol anesthesia. We investigated whether patients who underwent ioECoG-assisted epilepsy surgery remained under an adequate depth of sedation in the propofol administration free period based on postoperative reports of awareness and hemodynamic fluctuations during surgery. We aimed to identify which factors are associated with inadequate depth of sedation.

2. Methods

2.1. Patient selection

We retrospectively assessed all surgical cases of focal epilepsy in which ioECoG tailoring was performed at the UMC Utrecht in the period 2008–2019. We included all propofol-free periods (PFP) in which propofol administration was paused for ioECoG recording. PFP with the aim of awake functional mapping or PFP with missing data (e.g. hemodynamic data, propofol infusion data) were excluded.

2.2. Ethicalxxxx approval

All patients were participants of the *Registration database for Epilepsy surgery patients in the UMC Utrecht* (RESPect) database which is registered by the Medical Ethical Research Committee under protocol number 18-109. Patients who are included after 2018 gave informed consent for data collection. For all data before 2018, the need for informed consent was waived by the Medical Ethical Research Committee.

2.3. Surgical practice

Surgery was performed under general anesthesia using total intravenous anesthesia (TIVA) with propofol induction and maintenance. On induction of anesthesia, patients were given 100% oxygen. During maintenance, patients received a mixture of oxygen (30%) and air. No nitrous oxide was used in these patients. Propofol was combined with analgesics (sufentanil, remifentanil, alfentanil, morphine, pethidine or piritramide). Local anesthetics around the skin incision were not used. Antibiotic prophylaxis was administered according to the local protocol. Vasoactive drugs were administered if needed to maintain blood pressure between predefined limits (+/- 30% of normal blood pressure for the individual patient). Mannitol could be administered to reduce brain volume when indicated. Neurosurgeons performed craniotomies and placed the ioECoG electrodes directly on the brain cortex under the guidance of dedicated neurophysiologists. When the electrodes were in place, the anesthesiologists stopped or decreased the administration of propofol to 0 (most often) – 1 mg/kg/h depending on the individual preference of the anesthesiologist, while the administration of analgesics and the mixture of oxygen (30%) and air was continued. Vasoconstrictors, if used, could have been tapered during the PFP. Muscle relaxants(e.g., rocuronium) were sometimes used during surgery. Propofol administration was resumed when: 1) the ioECoG recording was completed or 2) clinical signs suspected of insufficient depth of sedation arose. The interpretation of such signs was observer-dependent but generally included intraoperative movements or a (rapid) rise in blood pressure and heart rate. Autonomic responses like tear and saliva production were not monitored. Surgical resection was tailored based on ioECoG findings. IoECoG recording is used to delineate the epileptogenic tissue, and this approach is personalized to each patient. The duration of ioECoG is mostly determined by the extent of the region that needs to be mapped. The electrode grid was placed multiple times on the cortex to cover the whole region of interest, which includes abnormalities on magnetic resonance imaging (MRI), Positron Emission Tomography – Computed Tomography (PET-CT), Single Photon Emission Computed Tomography (SPECT) and long-term invasive EEG monitoring. We generally aimed to record several minutes without burst suppression in each grid position. Therefore, propofol administration remained paused during the reposition of the grid until the delineation of the epileptic area was completed and was not resumed between the grid position changes.

2.4. Awareness and the depth of sedation

Awareness was defined as becoming conscious during a procedure performed under general anesthesia and subsequently having recalls of these events.(Mashour et al., 2011) We screened the operative reports, the intraoperative anesthesia records, and the reports from the postsurgical hospital stay and the outpatient clinic visits for recall of awareness. We used the change in mean arterial blood pressure (MAP; unit: millimeter of mercury (mmHg) and heart rate (HR; unit: beats per minute (bpm) as approximate indicators for possible inadequate depth of sedation. Intraoperative MAP and HR were automatically sampled by arterial catheters once per minute and recorded in the Anesthesia Patient Data Management system. Data reporting intraoperative movements, and drug administration by pump and by bolus injection were inserted manually into the same program during surgery. Clinical data such as age at surgery, sex, body mass index (BMI), American society of

anesthesiologist physical status classification system (ASA), and medical history of neurosurgical interventions were collected from electronic patient records.

We collected MAP, HR, and medication data from two periods during surgery: 1) the period between stopping and re-starting propofol administration (“propofol-free period = PFP”) and 2) the 10 min preceding PFP (“baseline”) (Fig. 1). The start of the PFP was defined as the time point when the propofol dosage was decreased to $\leq$ 1 mg/kg/h. The end of the PFP was defined as the time point when propofol administration regained its regular level or when a bolus of propofol was injected. We identified the maximum MAP and maximum HR during each PFP. We calculated the mean MAP and HR in the baseline period to determine the intraoperative baseline MAP and baseline HR for each patient. We calculated the percentage of change in MAP and HR during PFP compared to the baseline: change = (PFP – baseline)/baseline *100%. Based on the expert opinion of a dedicated neuroanesthesiologist (RH) and literature,(Kawasaki et al., 2018; Panousis et al., 2009) MAP and HR increase by more than 15% from baseline ($MAP_{INCREASE}$ and $HR_{INCREASE}$) were defined as potential indicators for inadequate depth of sedation.

We calculated the mean duration of the PFPs per surgery in two different ways depending on whether $MAP_{INCREASE}$ or $HR_{INCREASE}$ occurred in one or more PFP. In absence of $MAP_{INCREASE}$ or $HR_{INCREASE}$, the mean PFP duration per surgery was calculated as: mean PFP duration during surgery = $\sum$ duration of all PFP / total number of PFP. When $MAP_{INCREASE}$ or $HR_{INCREASE}$ did occur in one or more PFPs during surgery, we calculated the mean duration of PFP per surgery as: mean PFP duration during surgery = $\sum$ duration of all PFP with $MAP_{INCREASE}$ or $HR_{INCREASE}$ / number of PFP with $MAP_{INCREASE}$ or $HR_{INCREASE}$.

2.5. Statistical analysis

We report normally distributed continuous variables as means ± standard deviations (SD). We report patients below the age of three as a separate category as they respond differently to propofol than older patients. Categorical variables are presented in frequencies and percentages. On group level, we compared max MAP/HR during baseline vs. mean MAP/HR during PFP using a paired samples *t*-test. In addition, we compared the duration of PFPs with and without $MAP_{INCREASE}$ / $HR_{INCREASE}$ using an independent samples *t*-test. We used logistic regression models to investigate which variables were associated with having one or more PFP with $MAP_{INCREASE}$ or $HR_{INCREASE}$ during surgery. The variables identified from literature were age, sex, BMI, reoperation, ASA status, and the mean duration of PFP.(Wu et al., 2020) Clinical variables with a p-value of $\leq$ 0.2 in the univariable logistic regression analysis were included in the subsequent multivariable analysis. Multicollinearity was tested using linear regression. In case of multicollinearity, the least predictive variable was omitted from analysis. False discovery rate (FDR) correction on the p-values was performed to correct for multiple comparisons. A p-value of < 0.05 was considered statistically significant. Statistical analysis were performed in IBM SPSS Statistics 26 (IBM Corp., Armonk, NY) and statistical software RStudio, (version 2023.03.0). We used the STROBE cross sectional reporting guidelines (von Elm et al., 2008).

3. Results

3.1. Surgical procedures

We included 352 surgeries with 742 PFPs. On average, propofol was paused 2 ± 1 times per surgery (Table 1.). The average duration of the pause was 9 ± 5 min. The longest PFP lasted 32 min. During 29 PFP, drug boluses (alfentanil, morphine, remifentanil and sufentanil) were administered. Nineteen patients were under the age of three (5% of the complete cohort). The mean number of stops is 2 (±1) with an average PFP duration of 9 min (±4).

3.2. Awareness and depth of sedation

On a group level, the maximum MAP during PFP was higher than the mean MAP during the baseline period (70 ± 11 vs. 67 ± 9 mmHg; mean difference 3.0 mmHg 95% CI [2.7–3.3], p-value < 0.0005). HR was higher during PFP compared to baseline (68 ± 15 vs. 66 ± 15 bpm; mean difference 1.4 bpm 95% CI [1.2–1.5], p-value < 0.0005) (Table 1, Fig. 2 and supplementary figure 1). In the whole cohort, $MAP_{INCREASE}$ occurred in 54 PFPs across 51 surgeries. The majority (63%) of $MAP_{INCREASE}$ occurred during the first PFP. $MAP_{INCREASE}$ occurred in six patients under the age

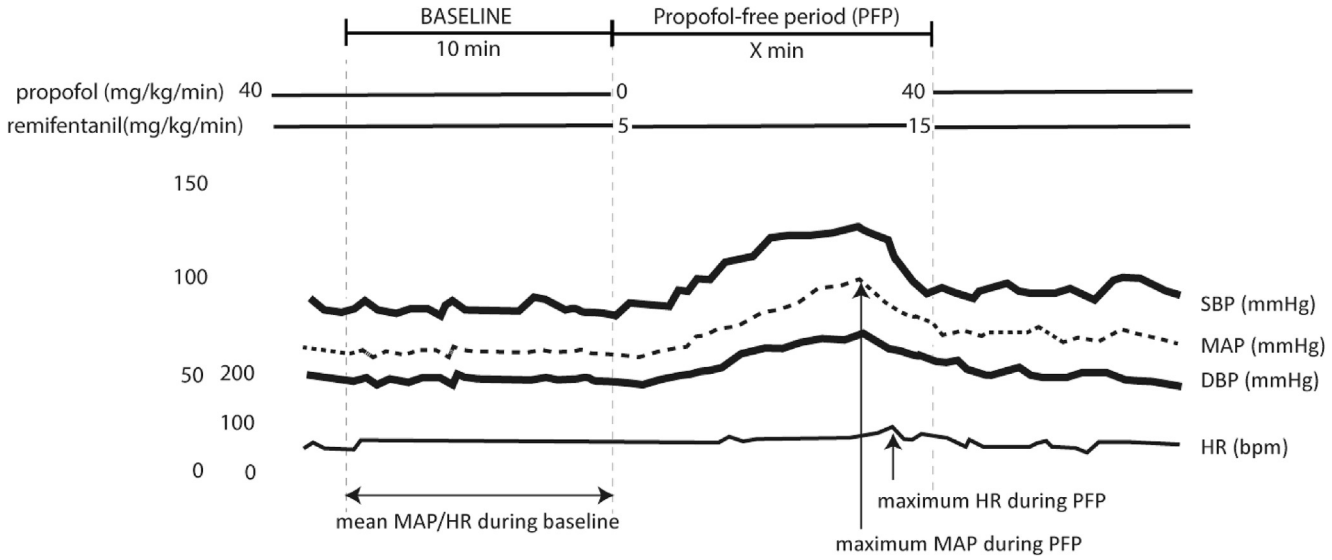

Fig. 1. Example of intraoperative anesthesiology data. Schematic representation of the variables as collected from the Anesthesia Patient Data Management system, including the continuous administration propofol and remifentanil, blood pressure (systolic (SBP), diastolic (DBP) and mean (MAP)) and heart rate (HR). The period between stopping and re-starting propofol administration was defined as “propofol-free period” (PFP) and the period 10 min before the PFP, as “baseline”.

Table 1
Baseline characteristics.

A. Patient characteristics (N=352)	
Age at surgery (y), mean ± SD	21.6 (±15.4)
BMI, mean ± SD	22.0 (±5.1)
Sex	
- Male	180 (51%)
- Female	172 (49%)
Epilepsy duration (y), mean ± SD (N=238*)	12.8 (±14.7)
Type of AED used prior to surgery**	
- Only benzodiazepines	221 (63%)
- Only non-benzodiazepines	0 (0%)
- Both non– & benzodiazepines	122 (35%)
- None	8 (2%)
Affected hemisphere	
- Left	161 (46%)
- Right	187 (53%)
- Missing data	4 (1%)
Anatomical location surgery	
- Temporal	231 (66%)
- Extra-temporal	117(33%
- Other (e.g. multifocal, other, missing)	4 (1%)
Underlying pathology	
- Mesial Temporal Sclerosis	25 (7%)
- CNS tumors (e.g. DNET)	92 (26%)
- Malformations of Cortical Development (e.g. FCD, MCD, TSC)	85 (24%)
- Other (e.g. cavernoma, gliosis)	53 (15%)
- No abnormalities	23 (7%)
- Dual pathology	35 (10%)
- Missing data ***	39 (11%)
ASA physical status (N=324****)	
- ASA I	56 (17%)
- ASA II	241 (74%)
- ASA III	27 (8%)
- ASA IV & V	0 (0%)
Re-operation	38 (11%)
B. PFP characteristics (N=742)	
Number pauses per surgery, mean ± SD	2 (±1)
PFP duration (min), mean ± SD	9 (±5)
Mean MAP in baseline (mmHg), mean ± SD	67 (±9)
Mean HR in baseline (bpm), mean ± SD	66 (±15)
Maximum MAP in PFP (mmHg), mean ± SD	70 (±11)
Maximum HR in PFP (bpm), mean ± SD	68 (±15)

Abbreviations: y = years, BMI=body mass index, AED=anti-epileptic drugs; ASA physical status = American Society of Anesthesiologist physical status classification, MAP=mean arterial pressure, HR=heart rate, * Epilepsy duration data was missing in 114 patients,** Our center's policy is that patients keep using their prescribed anti-epileptic drugs prior and during surgery, with the only exception being discontinuation of valproic acid (a non-benzodiazepine) prior to surgery, as it is associated with increased bleeding tendency. In relation to general propofol anesthesia, valproic acid increases the blood level of unconjugated propofol, hereby reducing the required propofol dose by 25–35%.*** Can be explained by re-operation and disconnection surgeries, as there is no need, insufficient or no possibility to retrieve a tissue sample for histopathology. **** ASA was not reported in 28 patients.

of three, which is significantly more frequently than the patients aged three years and older (31.6% versus 13.5%, p-value = 0.04, Fisher's exact test). Six PFPs showed $HR_{INCREASE}$ (0.8%) in six patients, all above the age three years. The incidence of $HR_{INCREASE}$ in patients under three was similar to patients older than three years (0% versus 1.8%, p-value 1.00, Fisher's exact test). All $HR_{INCREASE}$ occurred in the first PFP during surgery. Five patients (three male and two female; age 9, 18, 22, 35 and 50 years) exhibited both $MAP_{INCREASE}$ and $HR_{INCREASE}$ during PFP. Relevant medical history included 1x venous thrombosis, 1x idiopathic thrombocytopenia, splenectomy, portal vein thrombosis and postoperative sinus thrombosis. The underlying pathology in three out of the five patients was focal cortical dysplasia (left frontal, left parietal, and left temporal neocortex), and in the other two patients an arteriovenous malformation hemorrhage (right temporal neocortex) and perinatal asphyxia (right occipital neocortex). One of the patient moved his toes around the time that HR reached its peak value. As a response, the ioECoG recording was stopped immediately and the propofol administration was resumed. We found no clinical reports reporting awareness recall.

PFPs with $MAP_{INCREASE}$ were longer than those without $MAP_{INCREASE}$ (13 ± 6 min vs. 8 ± 5 min with the mean difference of 4 min 95%CI [3–6 min], $p < 0.001$). Similarly, PFPs with $HR_{INCREASE}$ were longer than the PFPs without $HR_{INCREASE}$ (14 ± 6 min vs. 9 ± 5 min with the mean difference of 6 min 95%CI [2–10 min], $p = 0.005$). Although the mean total duration of the PFPs with and without $MAP_{INCREASE}$ or $HR_{INCREASE}$ differed significantly, increased elapsed time after pausing propofol administration was not necessarily accompanied by hemodynamic changes (Fig. 3).

3.3. Variables associated with vital sign increase

The univariate analysis showed that an increased PFP duration was significantly associated with having a $MAP_{INCREASE}$ or a $HR_{INCREASE}$ during surgery ($p < 0.001$ ($p_{fdr} < 0.01$); OR 1.12 [1.11–1.26]), whilst a higher age showed only a potential trend ($p = 0.06$ ($p_{fdr} = 0.11$); OR=1.02, 95%CI [1.00–1.04]) (Table 2). Multivariable analysis revealed that a prolonged duration of PFP during surgery was associated with having a PFP with $MAP_{INCREASE}$ or $HR_{INCREASE}$ ($p < 0.001$ ($p_{fdr} < 0.01$);OR=1.18, 95%CI [1.11–1.26]) (Table 2). In other words, every minute without propofol administration was associated with an increased odd of 0.18 of having a $MAP_{INCREASE}$ or a $HR_{INCREASE}$ during surgery.

4. Discussion

We reviewed over 10 years of our institution's clinical experience in ioECoG-assisted epilepsy surgery, during which we, as part of our clinical routine, temporarily paused anesthesia to increase signal quality of the ioECoG. Propofol administration can be safely paused during epilepsy surgery to record ioECoG. In our relative big cohort (N=352), no signs of awareness were found in the patient reports after ioECoG-assisted epilepsy surgery in our study. Albeit, awareness recall might be underreported due to the retrospective character of the data review. We used hemodynamic changes (MAP and HR) after pausing the propofol administration to assess the depth of anesthesia. Five patients showed > 15% increase of MAP and HR during PFP. One of these patients also showed limb movements. This might indicate that the depth of sedation was too superficial at that moment. The propofol administration was resumed and the patient did not postoperatively report awareness. Our results suggested that signs of inadequate sedation depth after temporarily pausing propofol administration were rare, nor could we associate these instances with postoperative awareness recall.

The occurrence of $MAP_{INCREASE}$ and $HR_{INCREASE}$ during PFPs in surgery was associated with increased duration of the PFPs. Each minute without propofol administration was associated with an increased odd with an odd ratio 1.18; 95% CI [1.12–1.26], though prolonged PFP was not necessarily accompanied by hemodynamic changes. The average duration of the PFPs was nine minutes but could last up to 32 min without $MAP_{INCREASE}$ and $HR_{INCREASE}$. This result is expected as low dose of anesthetics is correlated with increased risk of awareness (Hardman and Aitkenhead, 2005; Spitellie et al., 2002). Albeit we always aim for a PFP as short as possible, in our experience there are two main factors that determine the duration of the PFP; 1.) the individual's response to propofol, in other words a "similar dose" of propofol can have substantially different effect on the initial EEG pattern observed, as well as the duration of weaning-off of the propofol in case of an

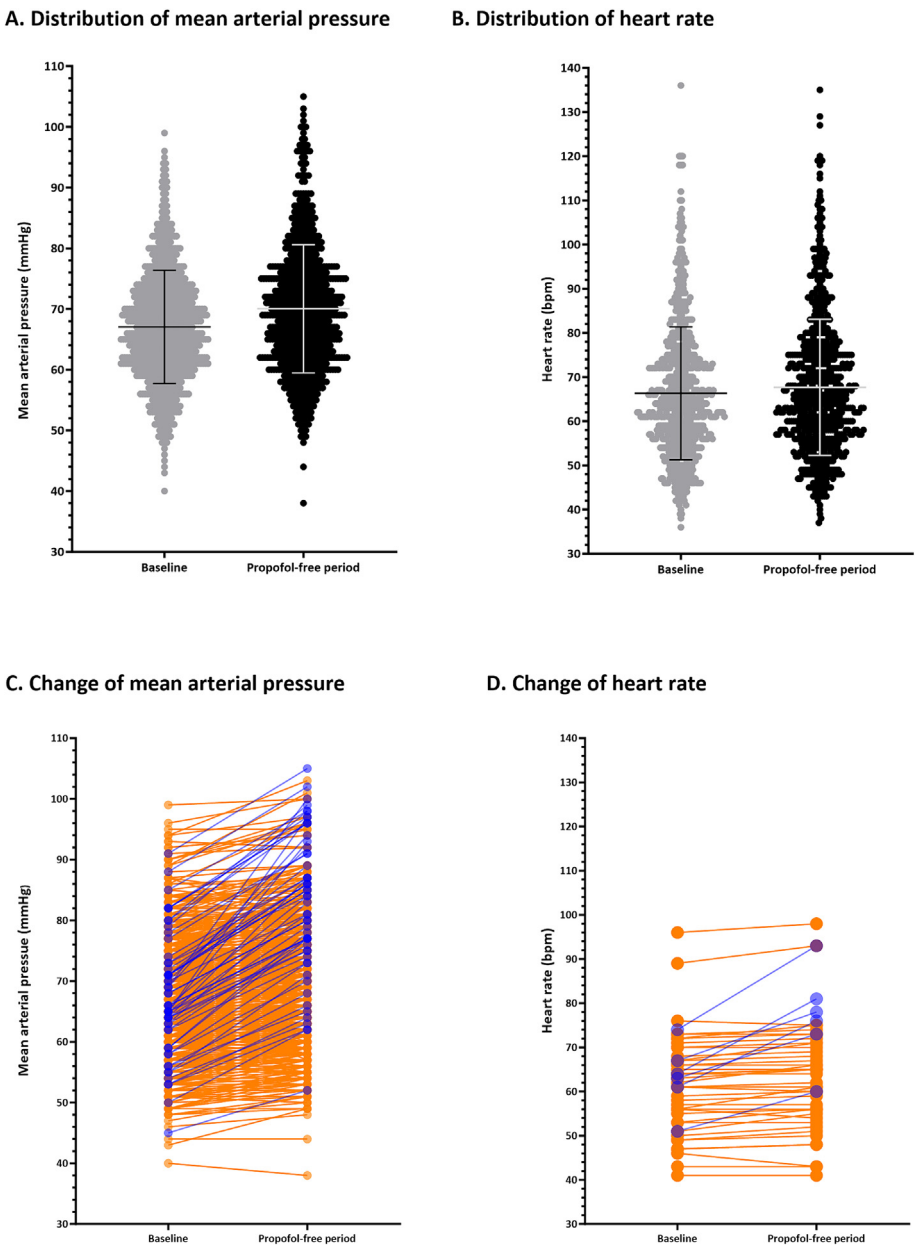

Fig. 2. Vital signs during the propofol-free period (PFP) and baseline. 2A: mean arterial pressure (MAP) in mmHg in the baseline period (gray dots) and during PFP (black dots) with marking of mean and standard deviation. 2B: heart rate in BPM in the baseline period (gray dots) and during PFP (black dots) with marking of mean and standard deviation. 2C: changes of MAP in mmHg between the baseline period and the PFP for all pauses within the cohort. In blue: changes for all pauses that demonstrated a clinically relevant increase of more than 15% in MAP during PFP compared to the baseline period. There is no decrease op > 15%. 2D: changes of heart rates in bpm between the baseline period and the PFP for all pauses within the cohort. In blue: changes for all pauses that demonstrated a clinically relevant increase of more than 15% in heart rate during PFP compared to the baseline period. There is no decrease > 15%. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

burst-suppression pattern, and 2.) the amount of anatomical locations to be sampled. One or both factors were usually in play in patients with PFP>20 min.

Adjusting the dosage of anesthetic drugs intraoperatively to optimize ioECoG recordings is common during epilepsy surgery. This procedure can be performed with either TIVA with propofol or with volatile agents such as sevoflurane or isoflurane (Greiner et al., 2016; Shah et al., 2018; Wu et al., 2010). In our study, propofol was used for induction and maintenance of general anesthesia in all cases because TIVA allows for smooth recovery of cerebral function after surgery and is thus preferred in our center. In our clinical experience, with decreasing a priori low propofol levels to propofol levels to 0 mg/kg/h, the burst suppression is either absent at the onset of the PFP or ceases within 5 min of recording. We assume that the results of our study would be applicable for inhalational anesthetics too since the risk of awareness is lower using inhalational anesthetics compared to TIVA: the incidence of awareness is 0.13–0.91% for inhalational anesthetics vs. 1.1% for TIVA. While end-tidal anesthetic agent monitor gives an estimation of the depth of sedation by inhalational anesthetics, the plasma drug concentration for propofol cannot be monitored in real-time and has wider interpatient variability (Errando et al., 2008; Hardman and Aitkenhead, 2005; Kuo et al., 2017; Morimoto et al., 2011; Parate et al., 2021; Spitellie et al., 2002). It is also important to note only limited studies on ioECoG-assisted epilepsy surgery reported on the details of their anesthetic procedure, while

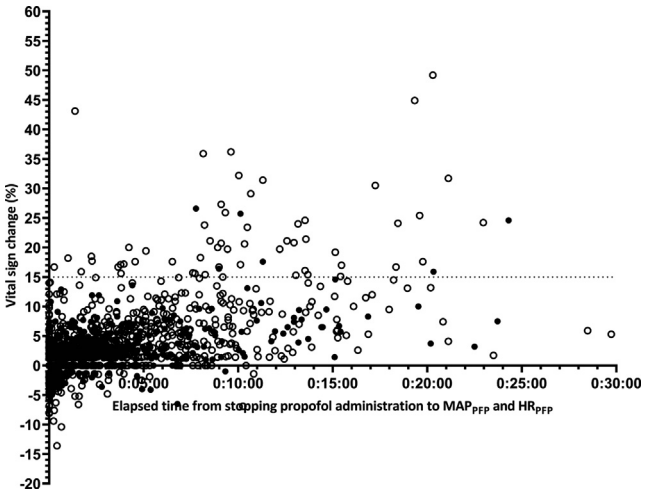

Fig. 3. Elapsed time from stopping the propofol administration to maximal MAP and HR during PFPs. The change (%) of MAP (circles) and HR (solid dots) in the PFP compared to baseline plotted against the elapsed time from pausing the propofol administration. The dotted line marks 15% (dotted line) increase. The maximum MAP and HR could occur at any giving moment after pausing propofol (0–30 min).

anesthetic information is crucial for the interpretation of the results.

We are the first to report on the procedure of pausing propofol administration to improve ioECoG quality and the safety of this technique in epilepsy surgery. The strength of this study is the large cohort under investigation and the availability of detailed, real-time information of intraoperative vital signs. Considering the exploratory character of this study, we deemed the use of a p-value of 0.2 for the univariable logistic regression as a cut-off variable for inclusion in the multivariable logistic regression acceptable. A major limitation is the retrospective assessment of awareness. Patients were not formally interviewed postoperatively for awareness during surgery. This might have led to an underestimation of the incidence of awareness as patients may not remember nor report awareness spontaneously (Errando et al., 2008). The trouble with determining the incidence of intra-operative awareness is that it is so infrequent, that it results in imprecise estimates. A recent Cochrane review (2019) reported an incidence of intraoperative awareness of nine per 1000 (1,1%) when anesthesia was guided by clinical signs.(Lewis et al., 2019) While Sandin et al. (2000) reported a lower incidence of 0.18% in cases in which neuromuscular blocking drugs were used, and 0.10% in the absence of such drugs (Sandin et al., 2000). Based upon these numbers, in our cohort of 352 patients, this would translate into an expected number of none to three cases of awareness besides the propofol pause. Even though the propofol is paused, the (restarting of) anesthesia was still guided by clinical signs.

An additional limitation is that we were not able to include Bispectral index (BIS) monitoring in our analyses which are not routinely performed in these surgeries. BIS monitoring has been proposed as a guide to optimize the depth of anesthesia. However, BIS values and ioECoG parameters during epilepsy surgery under anesthesia with propofol and fentanyl have a nonlinear correlation and are highly variable. While BIS values between 45 and 60 are considered optimal for most general anesthesia cases, it has been shown that BIS>60 is needed to avoid burst-suppression patterns in the ioECoG (Ramírez et al., 2017). BIS holds little superiority over clinical signs alone (Lewis et al., 2019), in particular in combination with ioECoG, as this records neuronal activity with high temporal and spatial resolution (Ramírez et al., 2017; Rampil, 1998). Changes in hemodynamics do not necessarily indicate awareness and the absence of changes does not guarantee unconsciousness. Furthermore, there is no uniform definition of clinically relevant hemodynamic changes. Blood pressure changes might be masked by the use of vasoactive drugs during surgery. We assumed that > 15% increase from baseline would be clinically relevant. We choose this stricter definition hemodynamic fluctuations compared to other studies to ensure there is no underestimation of possible awareness (Kawasaki et al., 2018; Panousis et al., 2009). Target-controlled infusion of propofol would offer more precise control of propofol administration. However, target-controlled infusion of propofol is not the standard method of drug administration during surgery at our center and could therefore not be included in our analyses. Another limitation is that we did not consider the effects of the administration of other supportive drugs during anesthesia, in particular vasoconstrictors, on the HR and MAP increase during the PFPs. We deliberately took this approach, what can be considered conservative, as this might have led to overreporting of HR/MAP increase.

Pausing propofol administration for ioECoG recording multiple times during epilepsy surgery is feasible without inducing high risks of intraoperative awareness. Albeit the number of awareness recall might be underreported in this cohort, in our opinion, the prospect of achieving seizure freedom by accurate ioECoG-assisted epilepsy surgery outweighs the probability of inducing

Table 2
Variables associated with MAP$_{INCREASE}$ or HR$_{INCREASE}$ during PFP.

	MAP$_{INCREASE}$ or HR$_{INCREASE}$ during surgery		**Univariate**		**Multivariate**	
Variables	**No (N=300)**	**Yes (N=52)**	**OR [95% CI]**	**p-value (p_{fdr})**	**OR [95% CI]**	**p-value (p_{fdr})**
Age (y), mean ± SD	21 (±15)	25 (±19)	1.02 [1.00–1.04]	0.06 (0.18)	1.19 [1.12–1.26]	0.12 (0.27)
BMI, mean ± SD	21.9 (±4.9)	22.8 (±5.8)	1.03 [0.98–1.09]	0.24 (0.43)	–	–
Sex						
- Male	155 (86%)	25 (14%)	1		–	–
- Female	145 (84%)	27 (16%)	1.15 [0.64–2.08]	0.63 (0.71)	–	–
ASA physical status						
- ASA I	51 (91%)	5 (9%)	1		–	
- ASA II	210 (87%)	31 (13%)	0.64 [0.31–1.33]	0.42 (0.57)	–	
- ASA III	20 (74%)	7 (26%)	1.1 [0.36–3.3]	0.88(0.88)	–	
First time surgery	266 (85%)	48 (15%)	1		–	–
Reoperation	34 (90%)	4 (11%)	0.65 [0.22–1.92]	0.44(0.57)	–	–
PFP duration (min), mean ± SD	9 ± 5	13 ± 5	**1.12 [1.11–1.26]**	**<0.001(<.01)**	**1.18 [1.12–1.26]**	**<0.001 (<0.01)**

Abbreviations: Significant results with a p-value < 0.05 (bold). Y=years, SD=standard deviation, OR=odds ratio, 95% CI=95% confidence interval, BMI=body mass index, ASA=American Society of Anesthesiologist physical status classification, PFP duration = mean duration of PFP during surgery, MAP$_{INCREASE}$=mean arterial pressure with > 15% increase, HR$_{INCREASE}$=heart rate with > 15% increase, p_{fdr} = false discovery rate(FDR) corrected p-value.

awareness during surgery. This procedure can be applied to improve ioECoG quality and subsequently postoperative seizure outcome. The duration of the propofol-free period was associated with hemodynamic changes during surgery, there is no fixed time point beyond which propofol administration must be resumed. On average, propofol administration was paused for 9 ± 5 min without evidence of causing awareness recall. In several cases propofol was paused for a longer period of time without complications. Our findings indicate that PFPs can be managed safely. A prerequisite will still be the continuous presence of the complete anesthesia team (anesthesiologist and anesthetic nurse or anesthesia technician) to handle any unforeseen events. A high level of awareness of any signs of early awakening of the patient is eminent. As always in anesthesia and in anesthesia training, it is a good thing to be prepared for problems even if you expect that these problems will not likely occur. Working with PFPs in neuro-anesthesia provides an opportunity to enhance the level of awareness for these mechanisms in the OR-team-members that are in training. Rapid reduction of anesthesia-induced ioECoG patterns and effective interpretation of epileptiform activity in ioECoG are crucial for optimal management of PFP. Future studies including target-controlled infusion of propofol are of interest to investigate the drug concentrations needed to achieve continuous ioECoG background patterns and allowing rapid cessation of burst suppression patterns, while maintaining an adequate level of sedation. In addition, future investigations into rapid automatic of epileptic biomarkers – which occur frequently during the interictal period – could aid intraoperative delineation of epileptogenic tissue and reduce PFP duration and subsequently the risk of awareness. By sharing our institution' s clinical experience, describing our clinical routine for intraoperative electrocorticography, we hope that this paper regarding the practice and safety of intraoperative electrocorticography can be used as guideline for centers that are not yet familiar with this procedure. The findings can be used to counsel patients in the presurgical trajectory.

Author contribution

D.S. and M.A.K were responsible for study conception and design, statistical analysis, figures & tables. E.M.R helped in data collection and data analysis. E.V.S. helped with RESPect patient recruitment, data collection and statistical analysis. F.S.S.L. was responsible for RESPect registry conception and design, and responsible for patient care together with P.C.R. M.D. was responsible for RESPect registry conception and design, patient recruitment and data collection. P.A.J.T.R as responsible for critical manuscript review and editing. R.G.H and M.Z.: helped in study conception and design, data interpretation, figures & tables. All authors were involved in drafting, writing or revising the manuscript and have read and approved the final version of the manuscript.

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Data availability statement

The data supporting the conclusions of this article will be made available by the authors upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2024.08.014.

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