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Propofol does not affect the reliability of early EEG for outcome prediction of comatose patients after cardiac arrest

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HIGHLIGHTS

- We studied the effects of propofol on the postanoxic EEG using visual and quantitative analysis.
- Propofol reduced amplitude, continuity, and dominant frequency and increased amplitude fluctuations.
- Propofol did not affect the reliability of EEG-based outcome predictions.

ABSTRACT

Objective: To quantify the effects of propofol on the EEG after cardiac arrest and to assess their influence on predictions of outcome.
Methods: In a prospective multicenter cohort study, we analyzed EEG recordings within the first 72 h after cardiac arrest. At six time points, EEGs were classified as favorable (continuous background), unfavorable (generalized suppression or synchronous patterns with ≥50% suppression), or intermediate. Quantitative EEG included measures for amplitude, background continuity, dominant frequency, and burst-suppression amplitude ratio (BSAR). The effect of propofol on each measure was estimated using mixed effects regression.
Results: We included 496 patients. The EEG after propofol cessation had no additional value over EEG-based outcome predictions during propofol administration at 12 h after cardiac arrest. Propofol was associated with decreased EEG amplitude, background continuity and dominant frequency, and increased BSAR. However, propofol did neither increase the chance of unfavorable EEG patterns (adjusted odds ratio (aOR) 0.95 per increase of 2 mg/kg/h, 95%-CI: 0.81–1.11) nor decrease the chance of favorable EEG patterns (aOR 0.98, 95%-CI: 0.89–1.09).
Conclusions: Propofol induces changes of the postanoxic EEG, but does not affect its value for the prediction of outcome.
Significance: We confirm the reliability of EEG-based outcome predictions in propofol-sedated patients after cardiac arrest.

1. Introduction

Postanoxic brain injury after cardiac arrest is among the most frequent causes of coma at the Intensive Care Unit (ICU). In approximately half of all patients, severe encephalopathy impedes recovery of consciousness. Patients are usually treated with targeted temperature management (TTM) at 32–36 °C and sedative medication for at least 24 h. Although this therapy may improve neurological outcome, it interferes with most methods for prognostication, such as the neurological examination (Sandroni et al., 2013).

Electroencephalography (EEG) is a reliable tool for prediction of outcome within the first 24 h after cardiac arrest, despite TTM and

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sedation (Sivaraju et al., 2015; Sondag et al., 2017; Spalletti et al., 2016). Previous studies showed that generalized suppression and synchronous patterns with ≥50% suppression (including generalized periodic discharges on a suppressed background and burst-suppression with generalized bursting and abrupt burst onsets, such as identical bursts) predict a poor outcome without false positives. EEG patterns with a continuous background, in the absence of rhythmic or periodic activity, have a strong association with good recovery (Sivaraju et al., 2015; Sondag et al., 2017; Spalletti et al., 2016).

Sedative medication affects the EEG. For example, propofol may induce burst-suppression patterns (San-Juan et al., 2010), and midazolam may reduce the EEG amplitude (Veselis et al., 1993) and can also induce burst-suppression (ter Horst et al., 2004). However, these EEG changes are typically induced at much higher doses than those used for sedation in the ICU (Huotari et al., 2004). Also, medication induced burst suppression has a different appearance than ischemia induced patterns (Hofmeijer et al., 2014).

An explorative study investigated quantitative EEG (qEEG) changes after sedation interruptions in relation to outcome (Drohan et al., 2018). Sedation altered EEG amplitude and continuity but did not importantly affect the relation between EEG parameters and neurological outcome. The sample size of this study was small, and the type of sedative medication and timing of the EEG varied widely.

In the current study, we focus on the effects of propofol, a commonly applied sedative drug at the ICU. We aim to quantify its effects on EEG patterns of comatose patients after cardiac arrest, and subsequent potential interference with outcome predictions. To that end, we quantify changes of the EEG shortly after cessation of propofol and assess whether these change the predictive value of the EEG. Furthermore, we estimate the effects of propofol on qualitative and quantitative EEG measures in multivariate models, and the probability of propofol inducing unfavorable EEG patterns.

2. Methods

2.1. Study design and participants

This is a retrospective analysis of a prospective cohort study conducted in five centers in The Netherlands. We used data from three participating centers (Medisch Spectrum Twente, St. Antonius Hospital, University Medical Center Groningen). Data from the other two centers were not used since continuous data on intravenously administered medication were not available. "Consecutive, comatose (Glasgow Coma Scale < 8), adult patients, admitted to the ICU after cardiac arrest, were considered eligible for inclusion. In all three centers, continuous EEG monitoring is considered standard care for comatose patients after cardiac arrest. Part of the EEG data were previously used for studies on outcome prediction after cardiac arrest using visual (Sondag et al., 2017) and quantitative analysis (Tjepkema-Cloostermans et al., 2017). The Medical Research Ethics Committee Twente waived the need for informed consent for the EEG monitoring. Informed consent was obtained from surviving patients at time of follow up." (Ruijter et al., 2018)

2.2. Standard of care

"Patients were treated according to standard protocols for comatose patients after cardiac arrest. A target temperature of 33 °C or 36 °C was induced as soon as possible after arrival on the ICU and maintained for 24 h. Patients were sedated with propofol, midazolam, or both, and received either morphine, fentanyl, or remifentanil for analgesia. Propofol sedation was usually interrupted after the period of TTM, and restarted in case of severe arousals, prolonged cooling to suppress fever, myoclonus, or seizures." (Ruijter et al., 2018)

2.3. Decisions on withdrawal of life-sustaining treatment

"Withdrawal of treatment was considered ≥72 h after cardiac arrest, during normothermia and off sedation. Decisions on treatment withdrawal were based on international guidelines including bilateral absence of somatosensory evoked potentials (SSEP), absent or extensor motor responses, and absence of brainstem reflexes (Sandroni et al., 2014; Wijdicks et al., 2006). Decisions on treatment withdrawal were sporadically taken between 48 and 72 h in case of absent SSEP responses. EEG data were not used for decisions regarding treatment withdrawal. However, physicians were not blinded to the EEG in order to allow for early detection and treatment of electrographic seizure activity." (Ruijter et al., 2018)

2.4. EEG recordings and analysis

"EEG recordings were started as soon as possible after admission to the ICU and, for practical reasons, only between 8 A.M. and 8 P.M. in each center, and not during weekend days in one center. Twenty-one cup electrodes were placed on the scalp according to the international 10–20 system. EEG recordings were continued until patients recovered consciousness or died, with a maximum of five days." (Ruijter et al., 2018)

All EEG analyses were performed offline, after the recordings. Visual analysis of EEG data was performed in a longitudinal bipolar montage, after band pass filtering (0.5 to 35 Hz). Five-minute EEG epochs were assessed at 6, 12, 24, 36, 48, and 72 h after cardiac arrest, as described before (Sondag et al., 2017), and at 1 ± 0.5 h before and after propofol sedation was stopped. EEG epochs were presented in random order to reviewers who were blinded to the timing of the epoch, the clinical condition of the patients, medication, and outcome. All EEG epochs were independently assessed by two experienced reviewers from a pool of six (B.R., M.T.-C., M.v.P., H.K., A.G., or J.H.). If the two reviewers disagreed, the final classification was determined by consensus. If necessary, a third reviewer was consulted. Reviewers were allowed to choose the option "no classification possible" if categorization of the epoch was considered unreliable due to artifacts.

On visual assessment, EEG patterns were classified as favorable (continuous), unfavorable (generalized suppression (all activity ≤10 μV) or synchronous patterns with ≥50% suppression), or intermediate. "Synchronous patterns with ≥50% suppression" included generalized periodic discharges on a suppressed background and synchronous burst-suppression, with generalized bursting and abrupt burst onsets. "Continuous" included normal amplitude (>20 μV) patterns with < 10% suppression and without periodic activity. "Intermediate" patterns included low voltage (maximum amplitude 10–20 μV), discontinuous (10–49% suppression or attenuation), heterogeneous burst-suppression (≥50% suppression or attenuation, without generalized bursting or abrupt burst onsets), and epileptiform patterns other than GPDs on a suppressed background.

Quantitative analysis of the EEG was performed every two hours between 2 and 72 h after cardiac arrest, and at 1 ± 0.5 h before and after propofol was first stopped. Five-minute, artifact-free epochs were extracted automatically by a computer algorithm at the desired time ±0.5 h. The algorithm selected the five consecutive minutes closest to the reference time with artifact-parameters below a desired threshold, as described before (Ruijter et al., 2018). No epoch was created if no artifact-free segment was found. For each EEG epoch, four qEEG features were

extracted, after application of a 6-th order Butterworth band pass filter with range 0.5–30 Hz: amplitude (AMP), defined as the root mean squared amplitude, background continuity index (BCI), defined as the fraction of EEG not spent in suppression (amplitude <10 μV for ≥0.5 s), burst-suppression amplitude ratio (BSAR), defined as the mean amplitude ratio between non-suppressed and suppressed segments (Ruijter et al., 2018), and alpha-delta ratio (ADR), defined as the power ratio between the alpha (8–12 Hz) and delta band (1–4 Hz). The BSAR was only calculated for BCI values between 0.05 and 0.95. Power spectral density was calculated using Welch's averaged periodogram with a 50% overlapping Hamming window of 10 s.

2.5. Additionally collected data

For each patient, information on timing and dosage of continuously administered medication in the first five days after cardiac arrest was extracted semi-automatically from the patient data management system (Metavision). Additionally collected data include age, sex, and resuscitation details.

2.6. Outcome

"The primary outcome measure was neurological functional recovery at six months, expressed as the score on the five-point Glasgow-Pittsburgh Cerebral Performance Category (CPC) (Cummins et al., 1991), dichotomized as good (CPC 1 or 2) or poor (CPC 3, 4, or 5). Outcome was assessed during a standardized telephone interview by one of two investigators (B.R. or M.T.-C.) or a trained research nurse. CPC scores were based on a Dutch translation of the EuroQol-6D questionnaire. In one center, CPC scores were assessed using the Short Form 36 (SF-36) questionnaire." (Ruijter et al., 2018)

2.7. Statistical analysis

In order to compare baseline characteristics of patients with good and poor outcomes, categorical variables were analyzed using Pearson's X^2-test, and continuous variables using the Mann-Whitney test. For analysis of the relation between propofol dose and the chance of a favorable or unfavorable EEG pattern, we used mixed-effects logistic regression. In the regression models, propofol dose at time of extraction of the EEG epoch plus the following co-variates were included as fixed terms: age, sex, location of cardiac arrest (in-hospital or out-of-hospital), initial cardiac rhythm (ventricular fibrillation (VF) or other), cause of cardiac arrest (cardiac or non-cardiac), time since cardiac arrest, midazolam dose at time of extraction of the EEG epoch, and an interaction term for midazolam and propofol doses. We included constant random effect terms for "patient" and "center".

For quantification of the effect of propofol on each of the qEEG measures, we used generalized linear mixed-effects regression with the same set of co-variates as used in the logistic regression analysis. In this analysis, we assumed a normal distribution of BCI and BSAR values, and gamma distributions for the AMP and ADR values. We used a logit link function to relate predictors to the BCI, and log link functions to relate predictors to AMP, BSAR, and ADR. For each model, we checked that residuals were normally distributed.

To compare the predictive value of the EEG during and after propofol sedation, we calculated test sensitivity and specificity (including 95% confidence intervals) at 12 h after cardiac arrest, at 1 ± 0.5 h before propofol cessation, and at 1 ± 0.5 h after propofol cessation. Additionally, we calculated odds ratios (OR) for good outcome for relevant EEG transitions after propofol cessation using logistic regression.

To compare qEEG features before and after cessation of propofol, we used Mann-Whitney tests. Additionally, we investigated quantitative EEG changes after cessation of propofol at an individual level. Since qEEG measures may to some extent fluctuate randomly over time, we tested each change for statistical significance. We defined a substantial increase as an increase greater than the 95th percentile value of changes between pairs of consecutive measurements not involved in a sedation transition. To compensate for ceiling and floor effects for the BCI, which could only take values between 0 to 1, we divided each change in the BCI by the maximum possible change. Similarly, to account for floor effects of the BSAR (with minimum value 1) we expressed decreases as fraction of the maximum possible decrease.

P-values < 0.05 were considered statistically significant. All tests were performed using Matlab Statistics Toolbox software (MATLAB and Statistics Toolbox Release R2017b, The MathWorks, Inc., Natick, Massachusetts, United States).

3. Results

Between May 2010 and November 2017, EEG recordings were started in 506 patients. Ten had no artifact-free EEG at any of the investigated time points, leaving 496 patients for the analysis. Twenty patients without available outcome data were only used for part of the analysis.

3.1. Clinical characteristics

Clinical characteristics are shown in Table 1, grouped by outcome. Poor outcome occurred in 269 patients (57%). Most differences were as expected: patients with poor outcome were older, more often had a non-cardiac cause of arrest, and less often had ventricular fibrillation (VF) as initial rhythm. Of note, patients with a good outcome received higher doses of sedation with propofol, fentanyl, and remifentanil. A minority of patients received both propofol and midazolam (12% of those with good outcome, 18% of those with poor outcome, p = 0.07). The median propofol dose was not different in those receiving midazolam as compared with those not receiving midazolam (3.0 vs. 3.2 mg/kg/h, p = 0.25).

Patients with good outcome more often had an interruption of propofol ≥1 h within the first 72 h than those with a poor outcome. In those with an interruption, the time to interruption and fraction in which propofol was restarted was not different between the outcome groups. For the quantification of EEG changes after cessation of propofol, we excluded 20 patients with poor outcome (7%) and 26 patients with a good outcome (13%) due to artifacts.

All patients with an unfavorable EEG pattern (generalized suppression or synchronous patterns with ≥50% suppression) at 12 h or later had a poor outcome (CPC 3–5). Of those with a continuous pattern at 12 h, 94% had a good outcome (CPC 1–2).

3.2. Qualitative changes of the EEG after propofol cessation

Fifteen patients had an unfavorable EEG pattern right before the cessation of propofol, and all of them had a poor outcome. In 10 of these cases (67%), the EEG remained unfavorable after propofol was stopped, and in 5 cases (33%) the EEG changed into a less specific, intermediate EEG pattern. Of the 171 patients with a favorable EEG during propofol sedation, 17 (10%) had an intermediate EEG pattern after the cessation of propofol and the others remained favorable. A transition towards an intermediate pattern decreased the chance of a good outcome (OR: 0.12, 95%-CI: 0.04–0.39). Of the 97 patients with an intermediate pattern during propofol sedation, 5 (5%) had an unfavorable pattern after

Table 1
Patient characteristics, grouped by outcome. Data are shown as number (percentage) or median (interquartile range). CA: cardiac arrest. SSEP: somatosensory evoked potential. VF: ventricular fibrillation. P-values indicate differences between patients with poor and good outcome.

	Poor outcome (CPC 3–5)	Good outcome (CPC 1–2)	P-value
Number	269 (57%)	207 (43%)	
Age	67 (55–74)	59 (50–69)	<0.001
Female	74 (28%)	49 (24%)	0.34
Out-of-hospital CA	235 (87%)	192 (93%)	0.05
Non-cardiac cause of CA	60 (26%)	12 (6%)	<0.001
VF as initial cardiac rhythm	135 (55%)	177 (88%)	<0.001
Therapeutic hypothermia (33 °C)	169 (63%)	138 (67%)	0.37
EEG start time (h after CA)	10 (5–18)	9 (5–16)	0.18
EEG stop time (h after CA)	56 (41–96)	52 (43–76)	0.69
Treatment with propofol	262 (98%)	204 (99%)	0.29
Max. dose in first 24 h (mg/kg/h)	3.0 (2.3–3.7)	3.5 (2.7–4.1)	<0.001
Treatment with midazolam	53 (20%)	25 (12%)	0.03
Max. dose in first 24 h (μg/kg/h)	63 (46–95)	68 (47–87)	0.66
Treatment with both propofol and midazolam	25 (12%)	49 (18%)	0.07
Treatment with fentanyl	160 (60%)	123 (60%)	1.00
Max. dose in first 24 h (μg/kg/h)	1.4 (1.1–2.1)	1.7 (1.3–2.4)	0.003
Treatment with remifentanil	33 (12%)	20 (10%)	0.37
Max. dose in first 24 h (μg/kg/h)	3.6 (2.5–5.6)	6.6 (3.4–11)	0.01
Treatment with morphine	54 (20%)	51 (25%)	0.23
Max. dose in first 24 h (μg/kg/h)	24 (17–29)	25 (21–29)	0.28
SSEP performed	177 (66%)	34 (16%)	<0.001
N20 bilaterally absent	74 (28%)	0 (0%)	<0.001
Propofol interruption >1 h within 72 h	170 (63%)	166 (80%)	<0.001
Time to propofol interruption (h)	40 (30–49)	41 (33–49)	0.09
Restart of propofol after interruption	110 (41%)	81 (39%)	0.70

cessation of propofol and 32 (33%) improved towards a favorable EEG pattern. The appearance of an unfavorable EEG pattern was invariably associated with a poor outcome, whereas improvement towards a favorable pattern increased the chance of a good outcome (OR: 12, 95%-CI: 3.8–38). Fig. 1 shows four examples of typical changes that took place after the cessation of propofol.

3.3. Additional prognostic information of the EEG after cessation of propofol

Among patients with EEG started within 12 h after cardiac arrest, the presence of an unfavorable EEG pattern after cessation of propofol did not allow identification of any new patients with poor outcome. After propofol cessation, the sensitivity of an unfavorable EEG pattern for poor outcome was 0.11 (95%-CI: 0.07–0.17), as compared to 0.48 (95%-CI: 0.40–0.55) at 12 h, at equal reliability.

After the cessation of propofol, predictions of good outcome did not change: the sensitivity of a favorable EEG increased not significantly (0.91, 95%-CI: 0.86–0.95 vs. 0.82, 95%-CI: 0.75–0.88) and its specificity decreased not significantly (0.65, 95%-CI: 0.57–0.72 vs. 0.69, 95%-CI: 0.61–0.76). Of note, at 12 h after cardiac arrest, the sensitivity of a favorable EEG for good outcome was lower than right before or after propofol cessation (0.40, 95%-CI: 0.22–0.48). However, its specificity was much higher (0.94, 95%-CI: 0.89–0.97), making the EEG at 12 h more useful for predictions of good outcome.

3.4. Quantitative changes of the EEG after propofol cessation and their prognostic value

Substantial changes in amplitude and background continuity after propofol cessation were associated with a good outcome (Fig. 2). The median amplitude of the EEG increased after the cessation of propofol in patients with good outcome (AMP: 10.7 vs. 8.99 μV, $p < 0.001$) but not in patients with poor outcome (8.47 vs. 5.63 μV, $p = 0.07$). Of note, patients with a good outcome more often had a substantial decrease of amplitude, too (10% vs. 3 %, $p = 0.02$). Both a substantial increase (OR: 2.46, 95%-CI: 1.36–4.44) and a substantial decrease in amplitude (OR 6.15, 95%-CI: 1.70–22.2) after propofol cessation were associated with good recovery, and added predictive value for good outcome prediction, as compared to the amplitude at 12 h.

Background continuity was higher after propofol cessation, both in patients with good outcome (BCI: 1.00 vs. 0.98, $p < 0.001$) and in those with poor outcome (median BCI: 0.93 vs. 0.75, $p = 0.04$). Again, the fraction of patients with a substantial increase was higher in the good outcome group (50% vs. 33%, $p = 0.01$).

The median alpha-delta ratio did not change after propofol cessation in patients with good outcome (ADR: 0.12 vs. 0.08, $p = 0.09$) or poor outcome (0.09 vs. 0.09, $p = 0.59$). There was no difference in the fraction of patients with a substantial increase in ADR between the outcome groups (16% vs. 10%, $p = 0.14$).

The amplitude ratio between bursts and suppressions (BSAR) did neither change in patients with good outcome (median BSAR: 2.77 vs. 2.81, $p = 0.15$) nor in patients with poor outcome (2.65 vs. 2.78, $p = 0.56$). The fraction of patients with a substantial increase or decrease was below 10% in both outcome groups.

3.5. Relation between administered propofol dose and observed EEG categories

In general, propofol dosages at 12 h after cardiac arrest were lower for patients with unfavorable EEG patterns as compared with patients with other EEG patterns (Fig. 3). The highest median doses were observed during discontinuous patterns, heterogeneous burst-suppression, and continuous patterns (2.85, 2.74, 2.67 mg/kg/h, respectively). Their median propofol dose was significantly higher than during synchronous burst-suppression (2.07 mg/kg/h, $p = 0.02$, $p = 0.02$, $p = 0.007$, respectively) and generalized suppression (1.94 mg/kg/h, $p = 0.01$, $p = 0.01$, $p = 0.01$, respectively).

In the multivariate model, propofol did neither decrease the chance of a favorable EEG pattern (adjusted odds ratio (aOR): 0.98 per increase of 2 mg/kg/h, 95%-CI: 0.89–1.09) nor increase the chance of an unfavorable EEG pattern (aOR: 0.95 per increase of 2 mg/kg/h, 95%-CI: 0.81–1.11). Midazolam was also not associated with the chance of a favorable or unfavorable EEG pattern. However, a combination of propofol and midazolam decreased the chance of a favorable EEG pattern (aOR: $7.7 \cdot 10^{-3}$, 95%-CI: $1.8 \cdot 10^{-4}$–0.33) (Fig. 4).

3.6. Relation between propofol dose and quantitative EEG measures

Higher propofol doses were associated with statistically significant changes of any of the qEEG measures (Fig. 5). For the median propofol dose at 12 h after cardiac arrest (2.66 mg/kg/h), the root mean squared amplitude (AMP) decreased with 23% (95%-CI: 12–33%), the background continuity index (BCI) decreased with 16% (95%-CI: 9–32%), the alpha delta ratio (ADR) decreased with 29% (95%-CI: 16–39%), and the burst-suppression amplitude ratio (BSAR) increased with 13% (95%-CI: 4–31%). Note that the

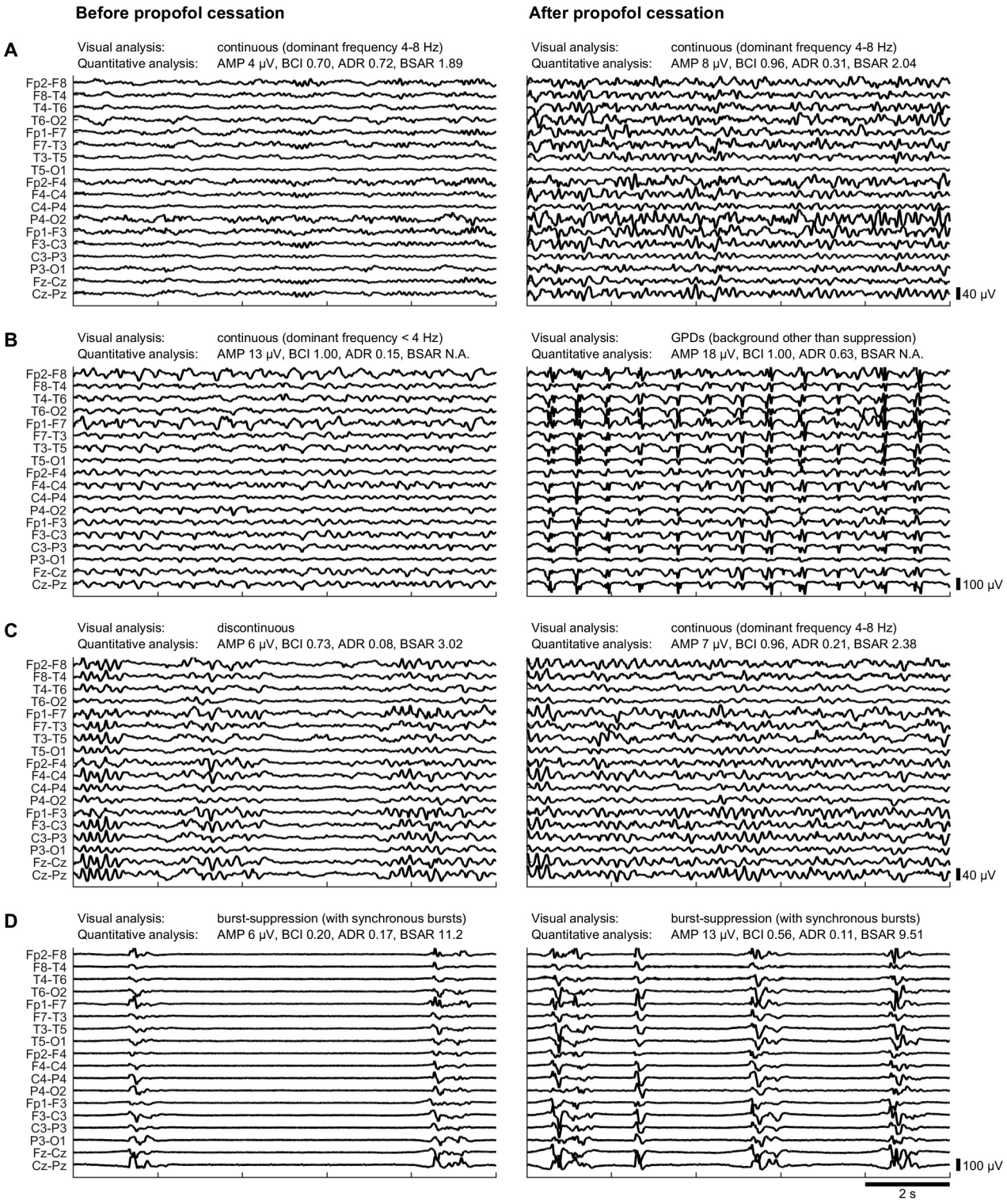

Fig. 1. Four examples of typical EEG changes after propofol cessation. Each subfigure shows a 10 s sample of EEG 1 ± 0.5 h before the cessation of propofol (left column) and 1 ± 0.5 h after the cessation of propofol (right column). Above each EEG sample, the category assigned after visual analysis is shown, plus the values of the quantitative EEG parameters, as calculated from the 10 s sample. A: Example from a patient with good outcome (CPC 1 at six months). The EEG remains continuous after propofol cessation, with a clear increase in amplitude and a change of dominant frequency. B: Example from a patient with poor outcome (CPC 5). After propofol cessation, GPDs appear from a continuous background pattern. C: Example from a patient with good outcome (CPC 2). The EEG becomes continuous after propofol cessation, without significant change in amplitude or dominant frequency. D: Example from a patient with poor outcome (CPC 5). After propofol cessation, the inter-burst interval decreases without significant changes to the bursts shapes or the background. AMP: amplitude, BCI: background continuity index, ADR: alpha-delta ratio, BSAR: burst-suppression amplitude ratio.

predicted effect sizes agree well with the order of magnitude of the observed changes in qEEG measures after cessation of propofol, as shown in Fig. 2.

Results were qualitatively the same in both outcome groups, indicating a lack of association between propofol induced EEG changes and outcome.

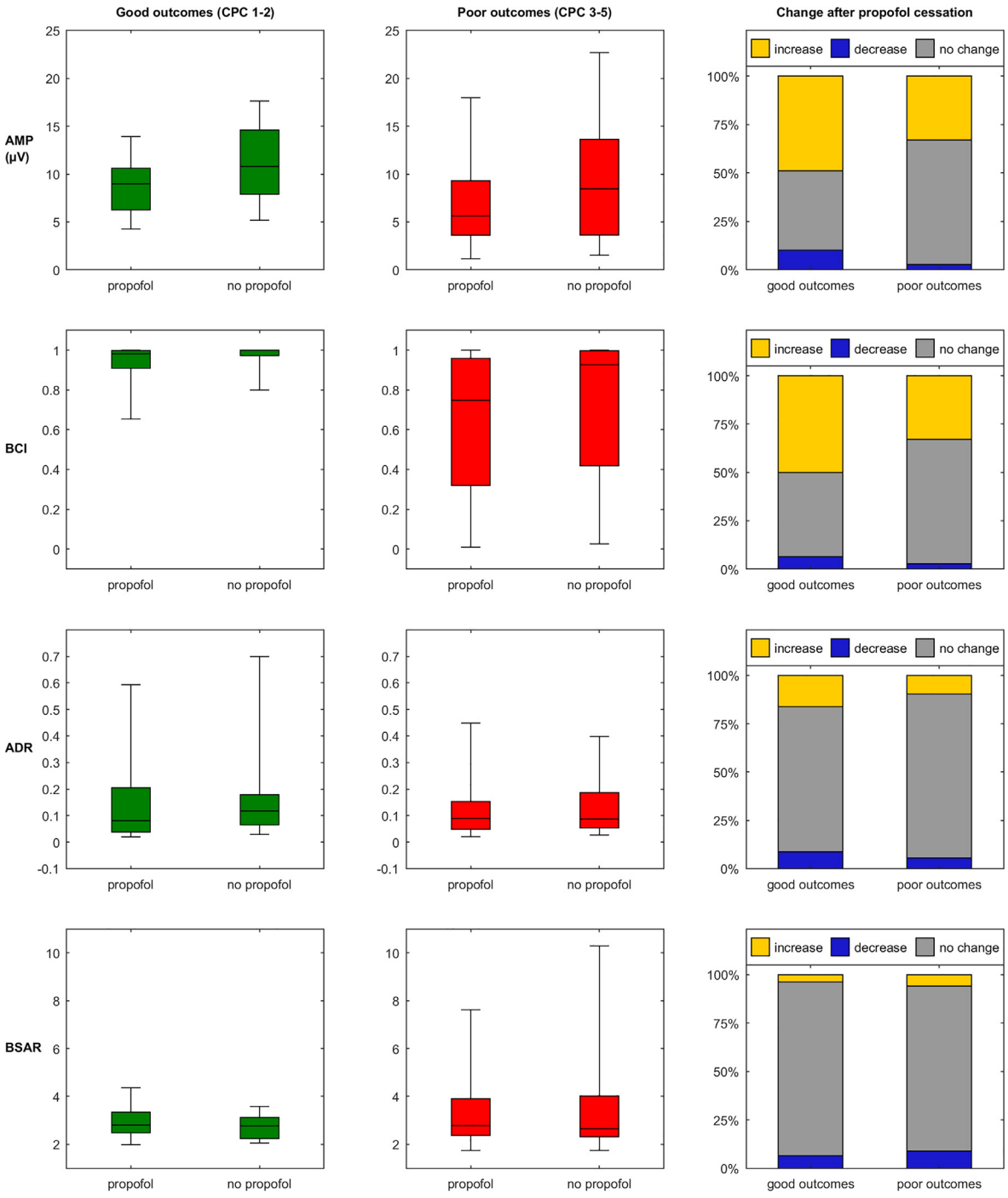

Fig. 2. Quantitative EEG changes after cessation of propofol sedation. Each row shows changes for one of the qEEG features. The first two columns compare the distribution of qEEG values, grouped by outcome, 1 ± 0.5 h before the first propofol interruption ('propofol'), and 1 ± 0.5 h after the first propofol interruption ('no propofol'). Horizontal lines indicate medians, boxes interquartile ranges, and error bars range from the 5th to 95th percentile values. The last column shows the fraction of patients with a substantial increase (>95th percentile of reference values) or decrease (<5th percentile of reference values). AMP: amplitude, BCI: background continuity index, ADR: alpha-delta ratio, BSAR: burst-suppression amplitude ratio.

4. Discussion

We investigated the effects of propofol sedation on EEG patterns of comatose patients after cardiac arrest, including the subsequent values for prediction of poor or good outcome. We show that propofol does neither decrease the chance of visually adjudicated favorable EEG patterns, nor increase the chance of unfavorable patterns, despite small quantitative effects on amplitude, background continuity, dominant frequency, and burst-suppression amplitude ratio. The EEG after propofol cessation, which took place at a median of 41 h after cardiac arrest, did not add to prediction of poor outcome. Quantitatively, increases in amplitude and background continuity after propofol cessation were more pronounced in patients with a good outcome.

Several studies have shown that EEG-based predictors of poor and good outcome of comatose patients after cardiac arrest are

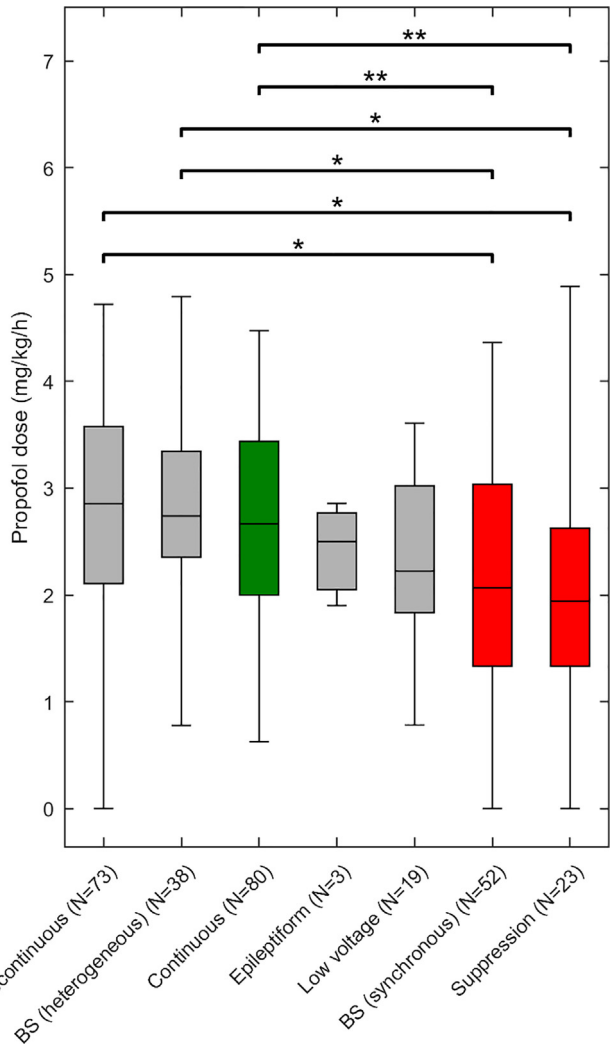

Fig. 3. Differences in propofol dose between EEG categories at 12 h after cardiac arrest. EEG categories are sorted by their median propofol doses, in descending order. Green boxes indicate favorable categories, red boxes unfavorable categories, and grey boxes intermediate categories. In each boxplot, horizontal lines indicate medians, the box the interquartile range, and the error bars the 5th and 95th percentile values. In the comparison of categories, * indicates $p < 0.05$, and ** indicates $p < 0.01$ for the difference, as determined by the Mann-Whitney test. BS: burst-suppression. Note that an EEG at 12 h after cardiac was available in 288 patients (58% of total). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

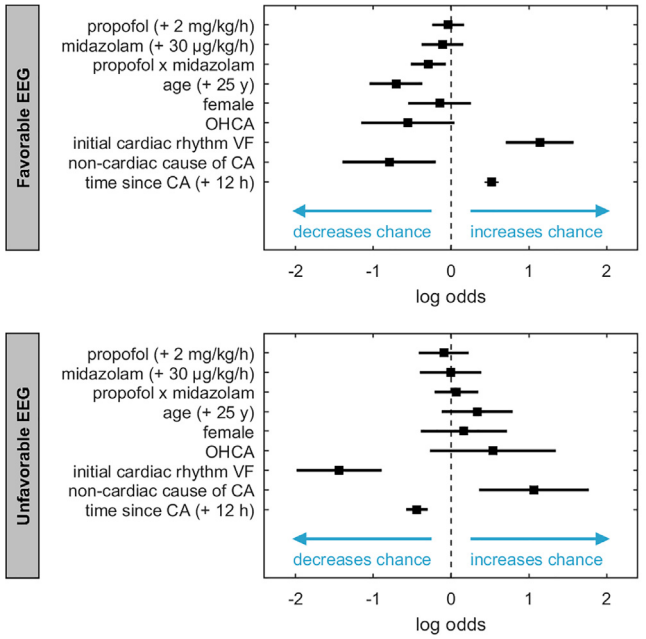

Fig. 4. Effects of individual predictors on chance of favorable and unfavorable EEG patterns in multivariate model. Squares indicate beta coefficients of the predictors, horizontal lines the corresponding 95% confidence intervals. CA: cardiac arrest, VF: ventricular fibrillation, OHCA: out of hospital cardiac arrest. "Propofol × midazolam" indicates the interaction effect between propofol and midazolam; the effect size refers to an increase in propofol dose with 2 mg/kg/h plus an increase in midazolam dose with 30 µg/kg/h.

robust, despite various treatment regimens with sedative medication. (Hofmeijer et al., 2015; Sivaraju et al., 2015; Sondag et al., 2017; Spalletti et al., 2016). However, since interpretation of the EEG critically depends on amplitude and background continuity, treatment with propofol or other sedative medication is often assumed to hamper the value of the EEG for outcome prediction. We now show that propofol sedation does not affect the reliability of the EEG for prediction of poor outcome.

The changes in the qEEG after propofol cessation confirm recent findings (Drohan et al, 2018), but we used a much larger sample with less heterogeneity in sedation regimes, better defined timing of EEG assessment, and a clear outcome measure. Our regression analysis allows for direction predictions of the effects of increasing propofol doses and the chance of observing favorable or unfavorable qEEG features and patterns during visual assessment.

On a group level, propofol doses were significantly lower in patients with unfavorable EEG patterns, as compared to patients with other EEG patterns. Most likely, this results from the fact that patients with severe brain injury have lower sedation requirements. Also, hemodynamic instability in severely affected patients may limit the maximum dose of propofol. Therefore, for the prediction of the qualitative and quantitative effects of propofol on the EEG, we included other predictors of the severity of brain injury as co-variates in our models. With respect to the qEEG measures, the agreement between the predicted effects and the observed effects after cessation of propofol suggest that the model is adequate.

In the range from 0 to 6 mg/kg/h propofol, the predicted decrease of background continuity by the linear mixed effects model was never more than 40%. This suggests that propofol, in the typical doses used, will on its own not induce burst-suppression patterns. For midazolam, we found no statistically significant effects. However, confidence intervals were large due to the small numbers of patients sedated with midazolam in our cohort.

This study has limitations. "As in all studies on outcome prediction of comatose patients after cardiac arrest, we cannot exclude a self-fulfilling prophecy (Geocadin et al., 2012). To minimize this risk, decisions on treatment withdrawal were based on international guidelines including bilaterally absent SSEP, absent or extensor motor responses, and absent brain stem reflexes (Sandroni et al., 2014). EEG patterns observed in the first 72 h after cardiac arrest were not taken into account." (Ruijter et al., 2018). In the regression analyses, where we related propofol doses to visual and quantitative EEG characteristics, we used medication doses during the recording of the epoch. Ongoing effects of medication administered before that time may have blurred our results to some extent. The fact that sedation interruptions for more than 1 hour were less often possible in patients with poor outcome may have biased our results on EEG changes after the cessation of propofol.

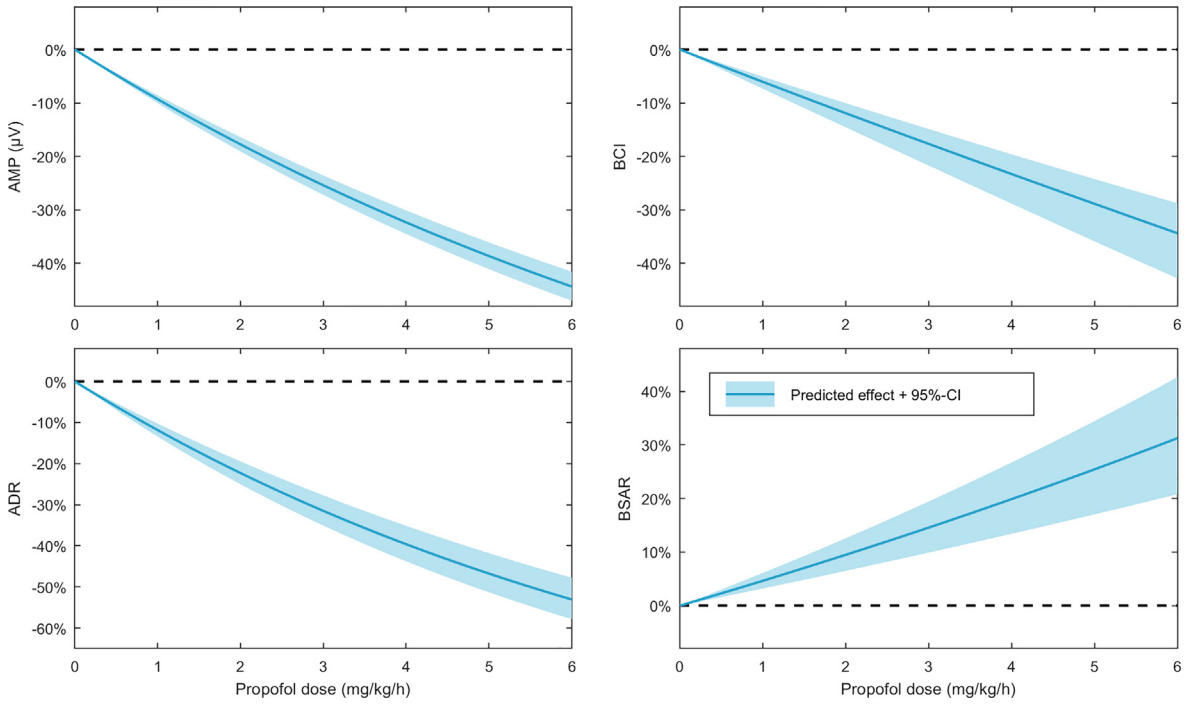

Fig. 5. Change of quantitative EEG measures for increasing propofol doses, as predicted by the linear mixed effect models. Solid lines represent the predicted change, shaded areas the corresponding 95% confidence intervals. AMP: amplitude, BCI: background continuity index, BSAR: burst-suppression amplitude ratio, ADR: alpha-delta ratio.

Declaration of Competing Interest

M.J.A.M. van Putten is co-founder of Clinical Science Systems, a supplier of EEG systems for Medisch Spectrum Twente. The other authors declare that they have no competing interests.

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