Article Title: Pilot study of propofol-induced slow waves as a pharmacological test for brain dysfunction following brain injury

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1

Competing Interests

A patent application has been filed by J. Kortelainen, E. Väyrynen and Tapio Seppänen on an apparatus and method for electroencephalographic examination (US14/674,318).

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Discussion: 1352

Abbreviated Title: Anesthesia, slow waves and brain dysfunction

Summary Statement: In this experimental pilot study, we found the comatose post-cardiac arrest patients with poor neurological outcome unable to generate normal propofol-induced electroencephalographic slow wave activity 48 h after cardiac arrest.

3

Abstract:

Background: Slow waves (< 1 Hz) are the most important electroencephalogram signatures of non-rapid eye movement sleep. While considered to have a substantial importance in, for example, providing conditions for single-cell rest and preventing long-term neural damage, a disturbance in this neurophysiological phenomenon is a potential indicator of brain dysfunction.

Methods: Since, in healthy individuals, slow waves can be induced with anesthetics, we tested the possible association between hypoxic brain injury and slow wave activity in comatose post-cardiac arrest patients (N = 10) using controlled propofol exposure. The slow wave activity was determined by calculating the low-frequency (< 1 Hz) power of the electroencephalograms recorded approximately 48 h after cardiac arrest. To define the association between the slow waves and the potential brain injury, the patients' neurological recovery was then followed for six months.

Results: In the patients with good neurological outcome (N = 6), the low-frequency power of electroencephalogram representing the slow wave activity was found to substantially increase (190 ± 83%, mean ± SD) due to the administration of propofol. By contrast, the patients with poor neurological outcome (N = 4) were unable to generate propofol-induced slow waves.

Conclusions: In this experimental pilot study, the comatose post-cardiac arrest patients with poor neurological outcome were unable to generate normal propofol-induced electroencephalographic slow wave activity 48 h after cardiac arrest. The finding might offer potential for developing a pharmacological test for prognostication of brain injury by measuring the electroencephalographic response to propofol.

Slow waves (< 1 Hz) are the most important electroencephalogram signatures of non-rapid eye movement (NREM) sleep.[1,2] This neurophysiological phenomenon originates from the neurons in the neocortex and thalamus which have been shown to exhibit slow (< 1 Hz) oscillations that correlate with the slow wave activity of electroencephalogram.[3] Even though slow oscillations are commonly still considered to be generated exclusively in the neocortex before spreading to the other brain areas,[4,5] compelling evidence highlights the thalamic contribution to their full electroencephalographic expression.[6-8] The physiological importance of the slow waves in higher cognitive function has convincingly been shown[9-11] and the lack of this electrophysiological phenomenon associated with disorders of consciousness[12,13]. In addition to the natural sleep, slow waves are seen in healthy individuals during general anesthesia. Originating from the same cellular and network level mechanisms as during NREM sleep,[14,15] anesthetic-induced slow waves are considered to be a product of an unconscious brain only occurring in deep sedation/anesthesia.[16] Recently, by using simultaneously recorded electroencephalogram and functional magnetic resonance imaging, the slow wave activity during anesthesia was shown to be related to the isolation of thalamocortical system from sensory stimulation and retention of internal thalamocortical exchange.[17]

Motivated by the physiological importance of the slow waves and the possibility to test their generation with anesthetics in a controlled manner, we hypothesized this electrophysiological phenomenon to be disrupted in an injured brain. The synchronized activity of large neuronal populations as well as the delicate interaction between cortical and sub-cortical areas required in the normal formation of the waves was expected to be sensitive to brain dysfunction. To test our hypothesis, we carried out an experiment with ten comatose patients treated in an intensive care unit (ICU) after cardiopulmonary resuscitation from out-of-hospital cardiac arrest. Because of the reduced oxygen supply during the event, the patients potentially suffered from hypoxic-ischemic brain injury due to which they had received therapeutic hypothermia treatment as a neuroprotective measure before the experiment. These patients generally represent a substantial diagnostic challenge as detecting the

5

potential diffuse brain injury in the early phase of recovery is highly demanding.[18] In the experiment, the patients' ability to generate anesthetic-induced slow waves was assessed 36–48 h after the insult with a pharmacological test in which they were exposed to varying amounts of anesthetic drug propofol in a controlled manner.

Materials and Methods

Experimental design

The experimental protocol was approved by The Regional Ethics Committee of the Northern Ostrobothnia Hospital District (decision 34/2012; March 28, 2012), Oulu, Finland, which follows the Declaration of Helsinki guidelines. The patients' closest relative was asked for an informed written consent for participations.

The study was carried out with ten comatose patients resuscitated from out-of-hospital cardiac arrest between May 2012 and April 2013 (Table 1). The sample size was selected to be appropriate for an experimental pilot study and no a priori statistical power analysis was conducted. We included patients with initial cardiac rhythm of ventricular fibrillation and persistent coma after the return of spontaneous circulation. The exclusion criteria were an age of less than 18 years, cardiogenic shock, possible causes of coma other than cardiac arrest (e.g. drug overdose, head trauma, or cerebrovascular accident), and earlier disease affecting the central nervous system. The subjects represented ten consecutive patients filling the inclusion criteria and no other selection was carried out. Before the experiment, the patients had received hypothermia treatment (33 °C to 34 °C for 24 h) according to the European Resuscitation Council guideline[19] as a neuroprotective measure. The experiment was carried out 36–48 h after the cardiac arrest when the hypothermia treatment had ended (body temperature > 35 °C) but the patients were still sedated and intubated. For sedation, we used a continuous intravenous infusion of propofol. In addition, eight of the patients received a low-dose infusion of analgesic fentanyl whose dosage was kept fixed during the experiment. The blood pressure was maintained with norepinephrine. Benzodiazepines such as midazolam were not used.

In the experiment, we recorded 19-channel electroencephalogram according to the 10/20 international system using an electrode cap with Ag/AgCl electrodes (impedance < 5 kΩ). For the recording, we used Nicolet nEEG Modular Neurodiagnostic System with a v32 Amplifier. The amplifier had a sampling frequency of 500 Hz and bandwidth of 0.053 – 125 Hz. For the reference, we used

common average. Before the recording, we maintained the patient's sedation with propofol given by an infusion pump following the ICU's common practice. During the experiment, we incrementally decreased propofol infusion rate following a predefined protocol (fig. 1) to determine the drug-induced changes in the slow wave activity at different anesthetic levels. We started the step-wise decrease from the highest acceptable infusion rate during the intensive care (4 mg x kg^{-1} x h^{-1}) and continued every 30 min until the drug administration was finally switched off. We used the same infusion rates (4, 3, 2, 1, 0.5, and 0 mg x kg^{-1} x h^{-1}) for all patients. For one patient, we excluded the highest infusion rate as the burst suppression pattern was already seen at the infusion rate 3 mg x kg^{-1} x h^{-1} and higher drug administration was thus not justified. We took a blood sample before each change in the infusion rate as well as in the end of the experiment, i.e. 30 min after turning propofol off, for the determination of plasma propofol concentration (fig. 1A). Plasma was separated within 30 min and stored at -70 °C until analysis. The concentration of propofol in plasma was determined by an approach utilizing liquid chromatography with fluorescence detection.[20] The day-to-day coefficient of variation (CV) of the method was 3.7% at 9.9 mg x l^{-1}, 3.5% at 0.96 mg x l^{-1} and 4.5% at 0.19 mg x l^{-1} (n = 4).

In addition to the experiment, we carried out several measures routinely used for the evaluation of brain injury and neurologic prognostication. As an electrophysiological test, we performed median nerve N20 somatosensory evoked potential measurement approximately 48 h after the cardiac arrest. We measured the neuron specific enolase as well as S100B protein immediately after the experiment and in the two consecutive days to improve the evaluation of possible neural injury. We also assessed the patients' neurological status throughout the ICU admission with clinical tests (corneal reflex, eye opening and movement, pupillary light reflex, verbal and motor behavior). The treating physicians were unaware of the result of the experiment and the treating decisions where thus not affected by the study.

We determined the severity of the hypoxic-ischemic brain injury by evaluating the neurological recovery six months after the cardiac arrest using the Cerebral Performance Category

(CPC, Table 2) as recommended by the American Heart Association.[21] We assigned the patients to either good (CPC 1–2) or poor (CPC 3–5) outcome groups based on if they were independent in activities of daily living after the follow-up period. If not clearly expressed in the patient files, we found out the recovery with a telephone interview with the patient or his/her relative.

Analysis of electroencephalogram

The signal processing of electroencephalogram (fig. 2) was carried out as follows. First, we extracted 5-min signal samples at each step of the drug infusion rate decrease. The samples were taken in the end of the 30-min period just before the change in the infusion rate as well as in the end of the experiment corresponding to the collection of the drug concentration blood samples. The electroencephalogram samples were evaluated for abnormalities such as epileptic activity or suppression as well as artifacts by a clinical neurophysiology specialist who was blinded to the experiment as well as the outcome of the patients. From each 5-min signal sample, 1–4 30-s representative sequences with minimal artifact were selected for further analysis. Some of these contained static electromyographic artifact which was, however, concentrated on the higher frequencies and thus did not disturb the analysis of slow wave activity. We filtered the selected 30-s signal sequences using a low-pass FIR filter with a cutoff frequency of 48 Hz before the calculation of a power spectral density (PSD) estimate using Welch's averaged periodogram method.[22] The estimates were created using a 5-s Hamming window and 4.9-s overlap. The window size was selected to be appropriate in capturing the slow waves while excluding the really low –frequency electrode potentials (< 2 Hz). We then calculated an average over the 1–4 PSD estimates representing the same infusion rate to improve the robustness of the estimate. From the average PSD estimate, we summed the components below 1 Hz to represent low-frequency electroencephalogram power. Finally, we calculated the average low-frequency power quantifying the patient's slow wave activity at certain infusion rate over the all 19 channels of electroencephalogram.

The computational electroencephalogram analysis was carried out with Matlab technical computing language, version 2011b (The MathWorks Inc.) and the topographic plots were made with EEGLAB v13.[23]

Statistical analysis

The effect of infusion rate and group (independent variables) on the average low-frequency power of electroencephalogram was statistically compared. In addition, the effect of these independent variables on plasma propofol concentration and blood pressure was analyzed. Repeatedly measured data was analyzed using Linear Mixed Model (LMM) with random intercept for subjects. The infusion rate –wise comparisons between groups were performed only if infusion rate x group interaction was significant ($P < 0.05$). For the statistical analyses, we used SAS (version 9.3. SAS Institute Inc., Cary, NC, USA).

Results

Patient outcome

Of the ten patients included in the study, six had good neurological outcome being, after the six-month follow-up period, independent in activities of daily living without any subjective neurological or psychological deficit due to the event (Table 1). Four of the ten patients, on the other hand, were eventually diagnosed with severe anoxic brain injury that led to permanent coma and finally death during the follow-up period.

Control measures for brain injury

Already with the small amount of patients included in this experimental study, the routine measures for brain injury were inconsistent with the outcome (Table 1). For example, absent N20 somatosensory evoked potential was detected only in half of the patients with poor outcome. Epileptic electroencephalogram and neuron specific enolase analysis produced, on the other hand, both false positives and false negatives in poor outcome classification point of view. These findings emphasize the diagnostic challenge related to the early-phase detection of the potential diffuse brain injury due to cardiac arrest.

Plasma propofol concentration

During the experiment, we decreased the amount of propofol administered by infusion step-wise from 4 to 0 mg x kg^{-1} x h^{-1} (fig. 1A). We measured the plasma drug concentration before every decrease of the infusion rate and in the end of the experiment (fig. 1A). The highest (infusion rate 4 mg x kg^{-1} x h^{-1}) and the lowest (infusion rate 0 mg x kg^{-1} x h^{-1}) individual drug concentrations during the experiment varied between 2.4 ± 0.4 (mean ± SD) and 0.98 ± 0.26 mg x l^{-1}, respectively. The individual concentration values at different propofol infusion rates are given in fig. 3. There was significant effect

of infusion rate ($P < 0.0001$) on the plasma propofol concentration. The effect of group ($P = 0.14$) and the infusion rate x group interaction ($P < 0.72$) were not statistically significant.

Slow wave activity

In the patients with good neurological outcome, the low-frequency (< 1 Hz) electroencephalogram power representing the slow wave activity was found to substantially decrease when the amount of propofol was reduced (fig. 1B-D and fig. 4). While the absolute effect was most pronounced in the prefrontal and temporal areas in which the slow wave activity was strongest at high propofol infusion rates (fig. 1D and fig. 5), a clear relative change was observed in all channels regardless of the brain region (fig. 1D and fig. 6A). The findings are in line with previous studies showing the propofol-induced low-frequency activity to occur widely across the whole scalp in healthy individuals.[16] Compared to the individual values at infusion rate 0 mg x kg^{-1} x h^{-1}, the propofol-induced increase in the low-frequency power at the maximum infusion rate (4 mg x kg^{-1} x h^{-1}) was $190 \pm 83\%$ (fig. 6B).

Unlike those who recovered well, the patients with poor outcome were unable to generate propofol-induced slow waves (fig. 4, fig. 5, and fig. 6). Decreasing the propofol infusion rate during the experiment did not markedly reduce the low-frequency electroencephalogram power. The power at the maximum infusion rate was $78 \pm 78\%$ compared to the individual values at infusion rate 0 mg x kg^{-1} x h^{-1} (fig. 6B). The average low-frequency powers at different infusion rates are given in fig. 4B. The effect of infusion rate ($P = 0.81$) and group ($P = 0.48$) on the average low-frequency power were not statistically significant. However, a significant infusion rate x group interaction ($P < 0.0001$) was observed leading to statistically significant difference between groups at infusion rate 4 mg x kg^{-1} x h^{-1} ($P < 0.01$) in the infusion rate –wise comparisons.

In the analysis, we also considered other factors possibly affecting the electroencephalographic recordings during the experiment and causing a difference between the groups. The patients with poor and good neurological outcome did not differ in age (64 ± 8 years and 65 ± 7

years, respectively). Furthermore, the effect of propofol infusion rate and group on blood pressures was analyzed (fig. 7). The infusion rate x group interaction on the systolic ($P = 0.32$), mean ($P = 0.39$), and diastolic ($P = 0.43$) blood pressures was not significant.

Visual evaluation of electroencephalograms

In addition to the computational analysis, the electroencephalograms were visually evaluated by a clinical neurophysiology specialist. Based on this evaluation, none of the patients with good or poor outcome had fully suppressed isoelectric electroencephalogram at any phase of the experiment. Burst suppression pattern was observed in nine of the ten patients focusing on the samples representing high propofol infusion rates whereas, in one patient with poor outcome, the signal was continuous during the entire recording. Clear epileptic activity was observed in three of the ten patients (Table 1), from which two (one with good and one with poor outcome) developed periodic epileptiform discharges as the propofol infusion was decreased. In addition, at low propofol infusion rates, one patient with poor outcome had sharp frontal theta transients indicating possible epileptic activity. For the patient with periodic epileptiform discharges and poor outcome, epileptic activity strongly affected the low-frequency electroencephalogram power measured at low infusion rates (fig. 4 and fig. 5). However, due to the anti-epileptic properties of propofol, the activity was suppressed in deeper anesthetic levels revealing the absence of background slow wave activity.

13

Discussion

In this experimental pilot study, we tested the ability of comatose post-cardiac arrest patients to generate normal propofol-induced electroencephalographic slow wave activity 48 h after cardiac arrest. Unlike those who recovered well, the patients with poor neurological outcome after a six-month follow-up period were unable to generate such activity.

In the current study, the changes in the low-frequency power of electroencephalogram were analyzed during a protocol in which the propofol infusion rate was incrementally decreased from the highest acceptable infusion rate in the intensive care to zero. The protocol was designed to bring out propofol-induced changes in the electroencephalogram as good as possible while taking into account the limitations related to the clinical setup. The conclusions of the study are based on the observation of the difference between groups during the protocol, more specifically, in high infusion rates. However, since the protocol could not be designed to achieve steady-state anesthesia at different infusion rates, the findings should be interpreted while taking into account the plasma propofol concentrations. This is especially important as the dataset only contained few samples with high propofol concentrations in the poor outcome group (fig. 4A). In healthy individuals, propofol-induced slow waves occur after loss of consciousness and increase to a saturation point as the anesthesia deepens.[17] After this, increasing the anesthetic effect starts to decrease the activity while the signal turns to the burst suppression pattern and finally isoelectric. With our protocol, nine of the ten patients (three of the four in poor outcome group) had suppression periods in their signal at high infusion rates meaning that these patients had already reached their saturation point in terms of slow wave activity. In other words, for these patients, increasing the anesthetic effect would not increase the slow wave activity. In one patient with poor outcome, the electroencephalogram was continuous throughout the recording. However, for this patient, the plasma propofol concentration at highest infusion rate was 1.63 mg x l^{-1}, representing a value at which nearly all of the patients with good outcome had already produced substantial slow wave activity

14

(fig. 4A). Consequently, it is unlikely that increasing the anesthetic effect in the patients with poor outcome would have increased their slow wave activity supporting the conclusion of the study.

Assessing brain function after an insult with potentially injurious effect to the brain, such as cardiac arrest, cerebrovascular accident, or traumatic brain injury, remains a substantial medical challenge. Appropriate treatment and development of new therapeutic interventions would benefit from reliable detection of brain dysfunction in the early phase of recovery.[24-26] On the other hand, an objective measure to avoid misdiagnosis of the vegetative state, for example, might later be needed.[27] It has been suggested that, instead of the laborious and expensive modern brain imaging techniques, the most practical screening tool for estimating brain function could be the century-old electroencephalogram.[28] Compared to the functional magnetic resonance imaging, for example, a clear benefit of electroencephalogram is, in addition to its price and availability, the possibility for bedside monitoring, an essential property especially for ICU patients.

If hypoxic brain injury fundamentally disturbs the neural system responsible for the generation of slow waves, as suggested by this experimental pilot study, this disturbance might be possible to reveal and use as a prognostic tool for irreversible damage by measuring the electroencephalographic response to propofol. Resulting from the rhythmic alternation of neocortical UP and DOWN states, slow waves are generated by periods of persistent, widespread network activity and collective neuronal silence, respectively.[29] Their full manifestation requires the sensory deafferentation achieved during anesthesia and NREM sleep[30-32] as well as retention of input from intrinsically oscillating thalamocortical neurons.[1,30,33] Whereas the exact mechanisms underlying the initiation and maintenance of the UP/DOWN state bistability have remained elusive,[29] the importance of this neurophysiological phenomenon for normal brain function has convincingly been shown.[9-13] Affecting virtually all neocortical neurons,[34] the slow oscillations are considered to have an essential role in providing conditions for single-cell rest and preventing long-term neural damage.[35]

Consequently, in addition to revealing an already existing injury, the lack of slow wave activity may also be a sign of an ongoing process having potential injurious effect itself.

Anesthetics are generally considered to disturb the interpretation of electroencephalogram. In addition to epileptiform activity, the recordings of patients with potential brain injury are assessed for unreactivity, burst suppression, and low voltage/flatness of the signal,[36] all of which may also partly or entirely be induced by general anesthetics like propofol. Consequently, for reliable analysis of electroencephalogram, minimization of the anesthetic delivery before signal interpretation is required causing difficulties especially in the early phase of the treatment. If the results of this pilot study can be confirmed with a larger dataset, this problem is turned upside down as it may indeed be a product of anesthetized and unconscious brain that helps in detecting the dysfunction and possible injury. The finding is particularly intriguing as, historically, anesthetic-induced coma has been applied to the patients at high risk for brain injury due to its potential neuroprotective effect.

Compared to the traditional electroencephalographic reactivity test, in which a response to an auditory or painful stimulation is observed, pharmacological testing could provide an objective and reproducible approach. Delivering the stimulus, i.e. administrating the anesthetic, does not involve subjective human activity like calling the patient by name or squeezing the trapezius muscle. Furthermore, the pharmacologically-induced activity could be more easily quantifiable measure and therefore independent of the investigator than the varying changes in the background frequency and amplitude seen in the electroencephalogram after an auditory or painful stimulus. Due to its conceptual similarity with the traditional electroencephalographic reactivity test and to be in line with the previous electroencephalogram terminology, we suggest this kind of a pharmacological approach to be called as electroencephalogram anesthetic reactivity test (ART).

Several steps need to be taken before the findings presented in this paper can be applied in the clinical practice. Firstly, and the most importantly, only a small amount of patients was included in this experimental pilot study requiring the validation of the results with larger datasets. The data was

emphasized to the both ends of the CPC scoring system meaning that the patients either recovered perfectly (CPC = 1) or died (CPC = 5) during the follow-up period. The applicability of the methodology in patients with CPC 2-4 should thus be validated as well. Furthermore, the study does not answer the question how early from the cardiac arrest the approach could be used to predict the outcome. Background electroencephalogram has been shown to substantially change during the first hours and days after the cardiac arrest. How does the reactivity of electroencephalogram to propofol change over time and at what point, if any, it reliably predicts the outcome is yet to be defined. To simplify its usage in the clinical environment, the method should also be further developed in terms of the anesthetic exposure. In the current study, the changes in the slow wave activity were assessed at decreasing amounts of propofol requiring a lot of time due to the slow wearing-off of the drug. However, our results suggest that it might be indeed the lack of slow wave activity at deep levels of propofol anesthesia that indicates brain dysfunction suggesting that the test could alternatively be carried out by exposing lightly sedated patients to higher amounts of propofol. While this would make the testing much quicker and consequently easier to be applied in the clinic, further investigations are required to confirm its validity. The generalizability of the results to different anesthetics should be examined as well. While one can hypothesize all of the general anesthetics with similar pharmacodynamics, i.e. gamma-aminobutyric acid -mediated inhibitory tone in the central nervous system, to produce similar results, these should be tested in separate clinical studies. Finally, reducing the number of electrodes to minimum would be highly appreciated when carrying out the measurement in the clinical environment. Based on the results presented, the propofol-induced relative increase in low-frequency power is topographically independent phenomenon (fig. 6A) suggesting that its absence could potentially be detected with significantly lower number of recording sites. This issue should be addressed in future studies.

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Table 1. Patient characteristics and measures for brain injury 48 h after cardiac arrest.

Patient	Gender	Age	Outcome	Fentanyl infusion	Epileptic EEG	Absent N20 SEP	NSE > 33 µg l⁻¹
1	M	63	Poor	x	x		x
2	M	54	Poor			x	x
3	M	72	Good	x			
4	M	59	Good	x			x
5	M	67	Poor	x			
6	F	55	Good				x
7	M	66	Good	x			
8	M	73	Poor	x	x	x	x
9	M	67	Good	x			
10	M	72	Good	x	x		

EEG = electroencephalogram; SEP = somatosensory evoked potential; NSE = neuron specific enolase.

Table 2. Cerebral Performance Category (CPC).

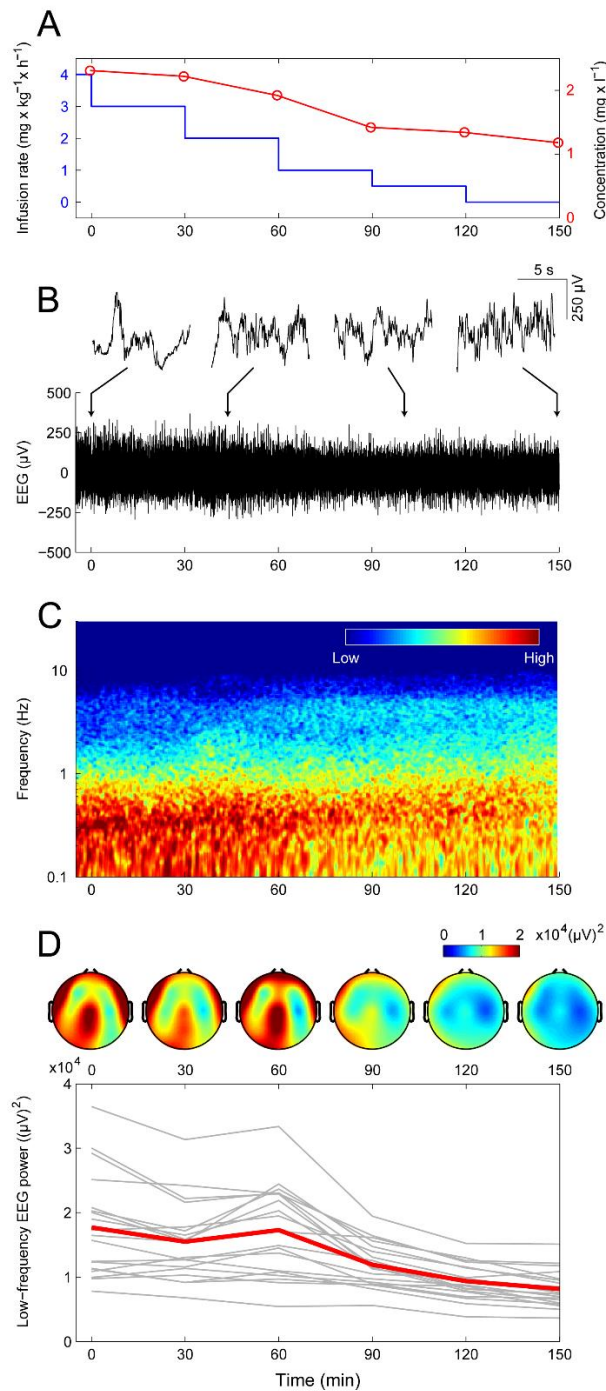| CPC 1	Return of normal cerebral function and normal living
CPC 2	Disability but sufficient function for independent activities of daily life
CPC 3	Severe disability
CPC 4	Coma
CPC 5	Death

Fig. 1. Effect of propofol on electroencephalogram (EEG) slow wave activity in a single patient with good neurological outcome. (A) Propofol infusion rate (blue line) and corresponding measures of plasma propofol concentration (red line) during the experiment. The infusion rate was decreased step-wise every 30 min and the drug concentration was determined on every step just before the next decrease as well as in the end of the experiment (red circles). (B) Raw EEG of a single channel (F7) during the experiment. Four 10-s signal samples from different phases of the experiment are presented above the whole signal. (C) Power spectral density as a function of time for the signal given in (B). The frequency axis is given in logarithmic scale. (D) Low-frequency (< 1 Hz) EEG power representing patient's slow wave activity during the experiment. The average low-frequency power (red curve) is calculated from all 19 single channel powers (gray curves). The topographic distribution of the low-frequency EEG power at different phases of the experiment is given above the curves.
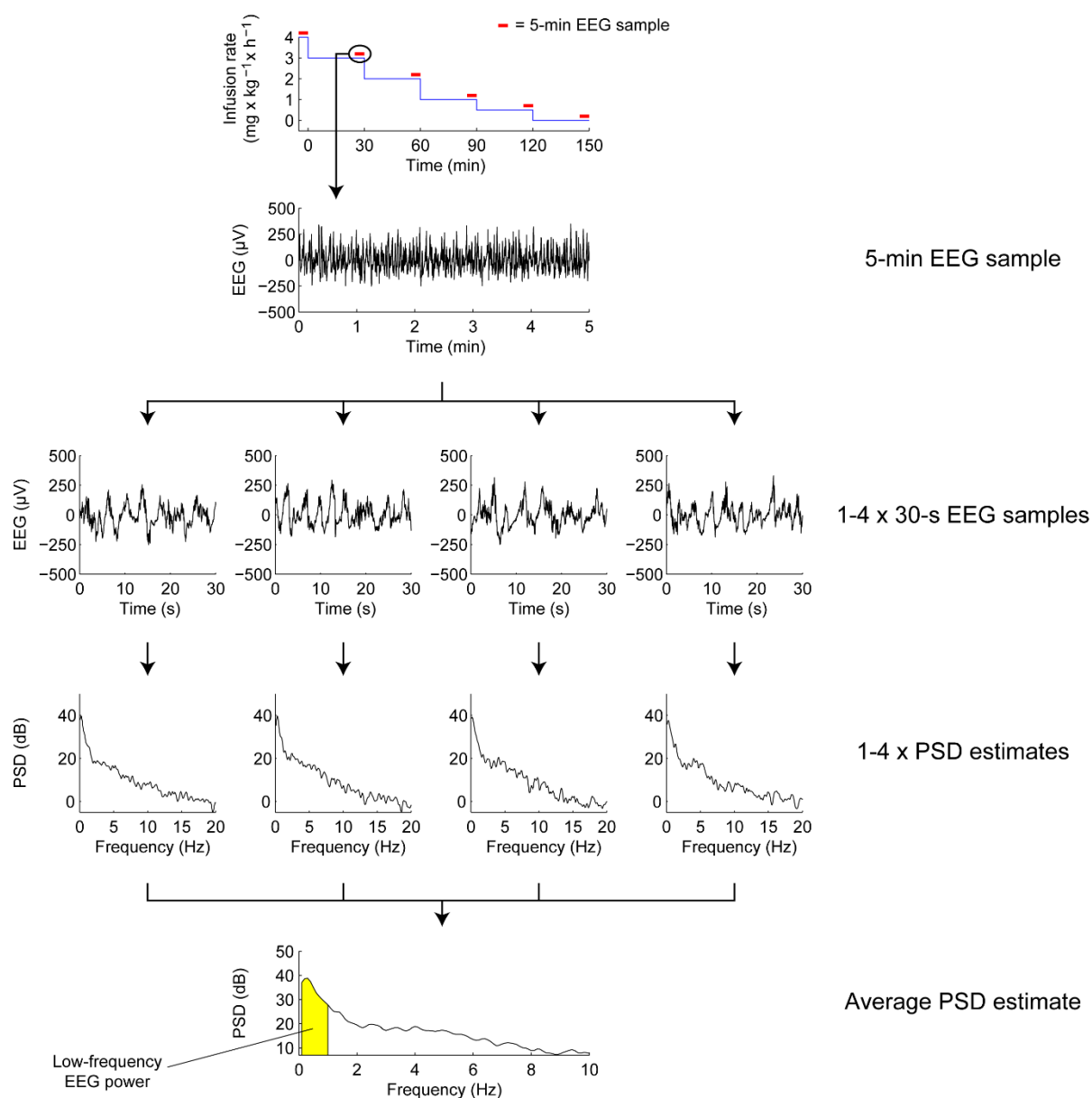
Fig. 2. Electroencephalogram (EEG) signal processing steps. First, 5-min signal samples at each step of the drug infusion rate decrease were extracted. From each 5-min signal sample, 1–4 30-s representative artifact-free sequences were selected for further analysis. Next, the power spectral density (PSD) estimates were determined for each 30-s sequences. Finally, an average over the 1–4 PSD estimates was calculated, from which the components below 1 Hz were summed to represent low-frequency EEG power.
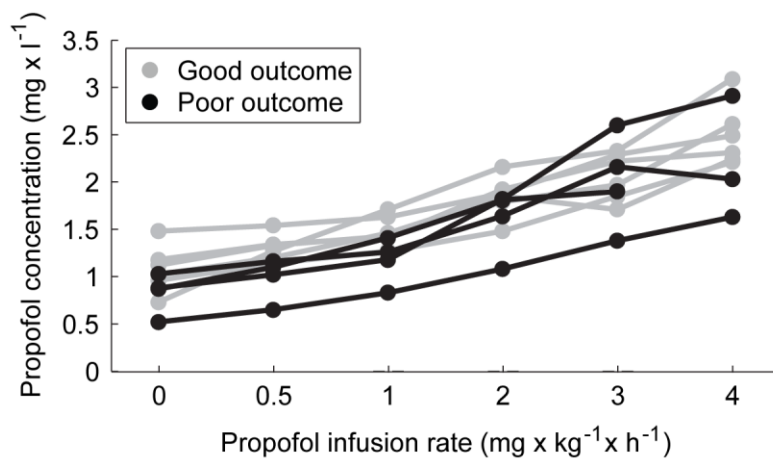
Fig. 3. Plasma propofol concentrations at different infusion rates for patients with good (N = 6) and poor (N = 4) neurological outcome. The samples of each individual are connected with lines.
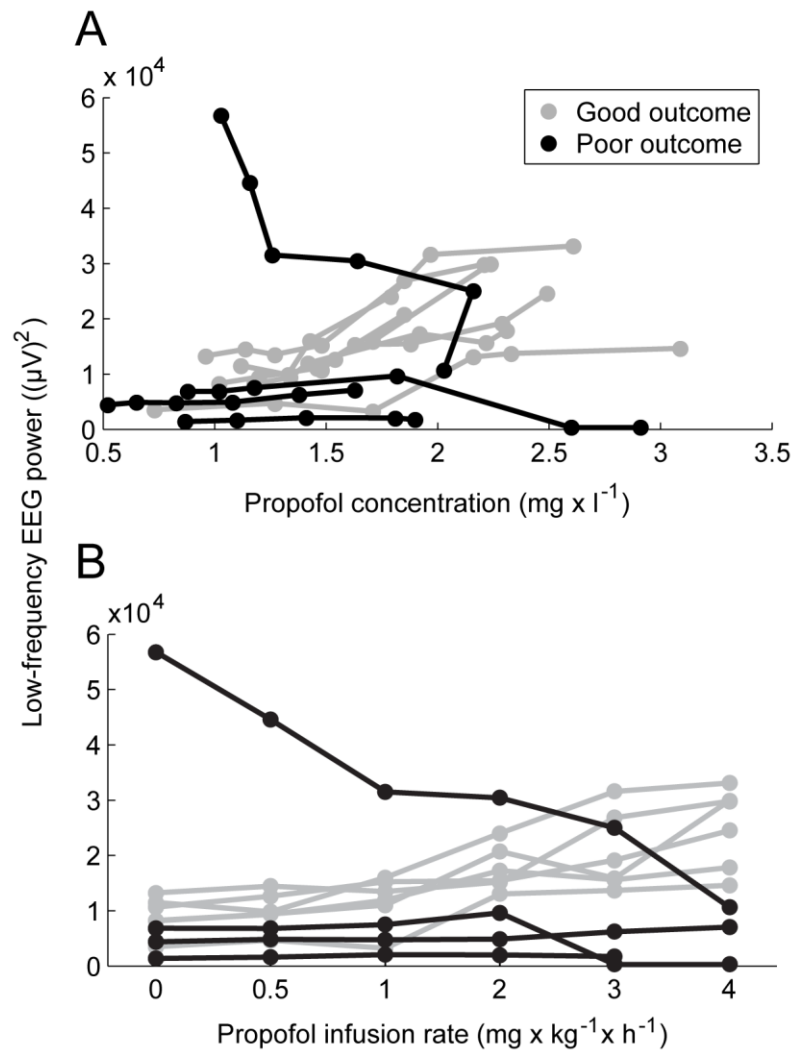
Fig. 4. The effect of propofol on low-frequency electroencephalogram (EEG) power. (A) Plasma propofol concentration and low-frequency EEG power for patients with good (N = 6) and poor (N = 4) neurological outcome. The values are individual average powers calculated over the all 19 EEG channels. The samples of each individual are connected with lines. For one patient with poor outcome, periodic epileptiform discharges, emphasized at low concentrations, strongly affected the low-frequency electroencephalogram power. (B) Average low-frequency EEG power at different propofol infusion rates.
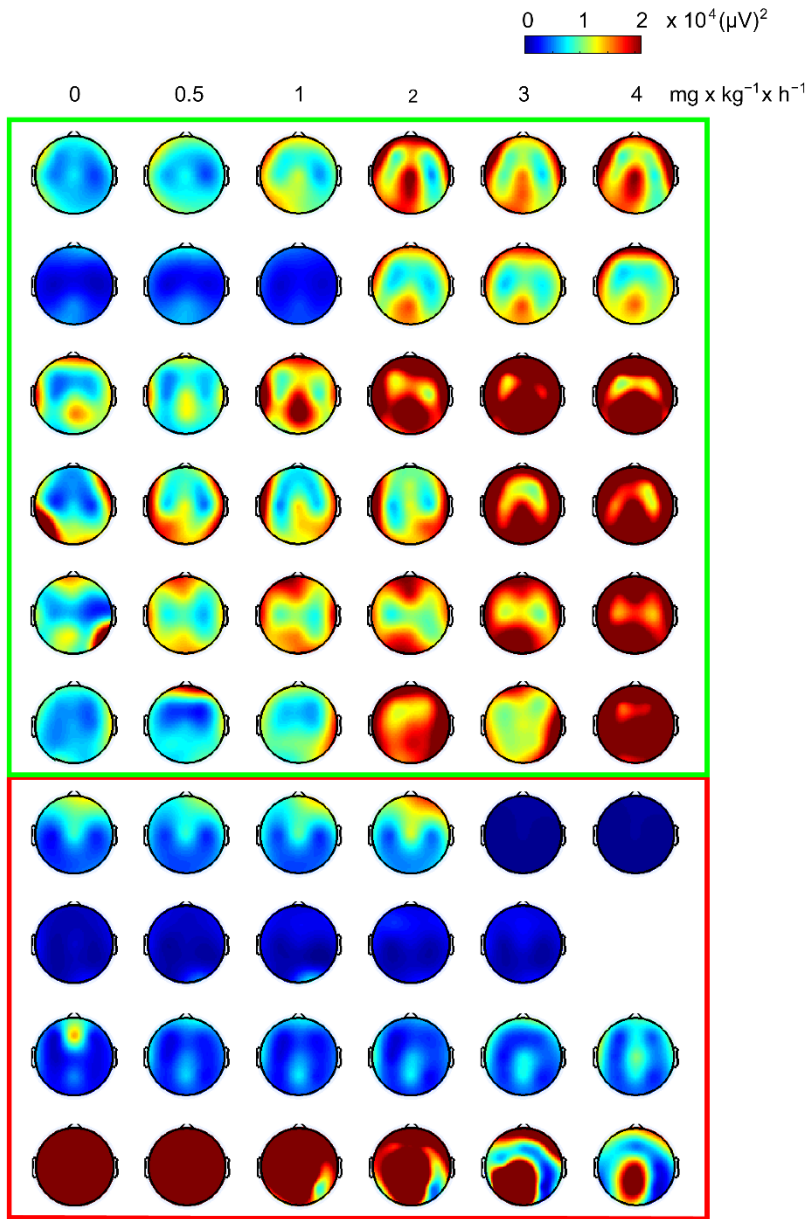
Fig. 5. Individual topographic distributions of low-frequency activity at different infusion rates. Rows represent different patients and column different infusion rates. The patients with good neurological outcome (green border) are above those with poor outcome (red border). The values are absolute low-frequency (< 1 Hz) powers.
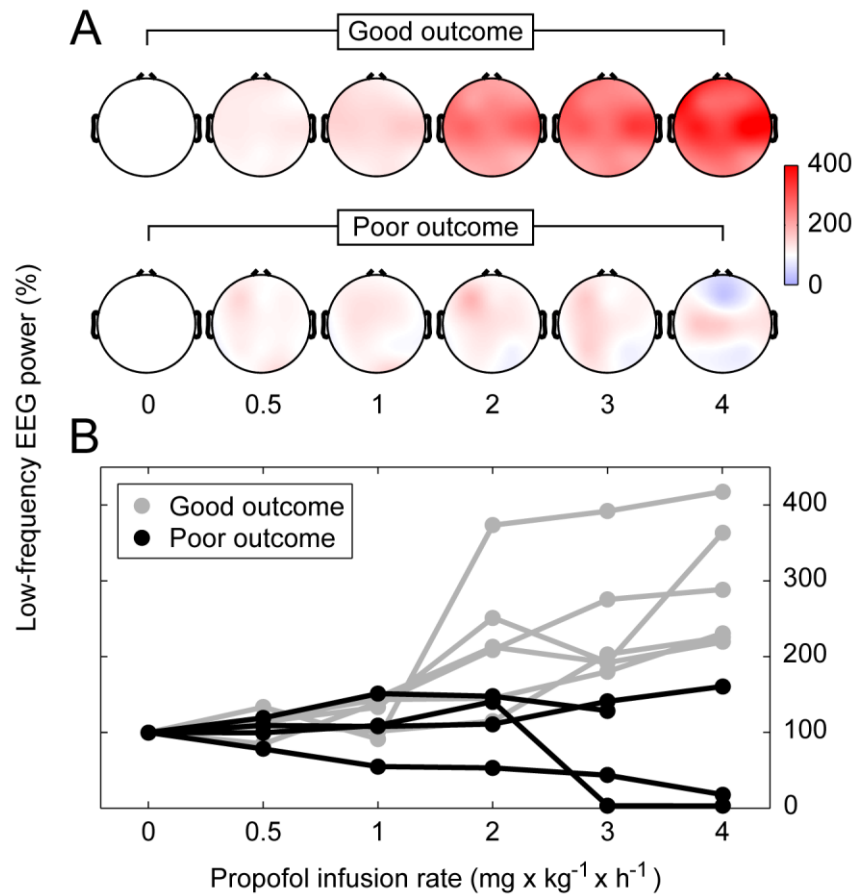
Fig. 6. Propofol-induced slow wave activity in patients with good and poor neurological outcome. (A) Topographic distribution of low-frequency (< 1 Hz) electroencephalogram (EEG) power representing slow wave activity at different propofol infusion rates. The distributions are averages calculated separately for the patients with good (N = 6) and poor (N = 4) neurological outcome. The values are given in percentages relative to the individual channel-wise powers at the propofol infusion rate 0 mg x kg^{-1} x h^{-1}. (B) Low-frequency EEG power at different propofol infusion rates for patients with good (N = 6) and poor (N = 4) neurological outcome. The values represent individual average powers calculated from all 19 channels given relative to the individual average power at propofol infusion rate 0 mg x kg^{-1} x h^{-1}. The samples of each individual are connected with lines.
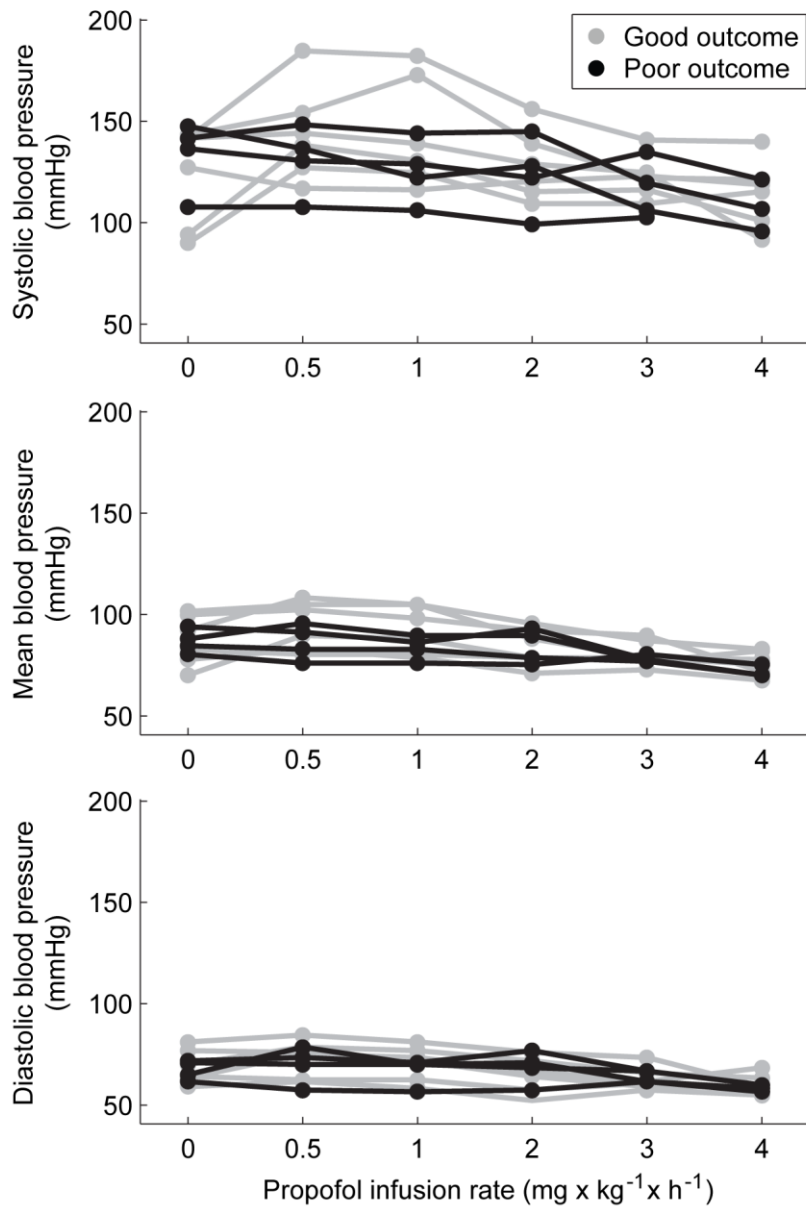
Fig. 7. Blood pressure at different propofol infusion rates for patients with good (N = 6) and poor (N = 4) neurological outcome. The samples of each individual are connected with lines.